

10/660,763

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(FILE 'HOME' ENTERED AT 12:43:08 ON 02 AUG 2005)

FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS, LIFESCI' ENTERED AT 12:43:44 ON 02 AUG 2005

L1 219065 S TYROSINE (A) KINASE?
L2 117272 S PROTO(W) ONCOGENE
L3 19359 S L1 AND L2
L4 11988 S HUMAN AND L3
L5 7194083 S CLON? OR EXPRESS? OR RECOMBINANT
L6 8010 S L4 AND L5
L7 1361302 S UTERUS OR LEUKEMIA OR ADENOCARCINOMA
L8 1451 S L6 AND L7
L9 5 S L8 AND HIPPOCAMPUS
L10 67 S L2(W) L1
L11 33 DUP REM L10 (34 DUPLICATES REMOVED)
E GAN W/AU
L12 98 S E3
E DIFRANCESCO V/AU
L13 97 S E3-E4
E BEASLEY E M/AU
L14 330 S E3
E YE J/AU
L15 1947 S E3
L16 2366 S L12 OR L13 OR L14 OR L15
L17 1 S L4 AND L16
L18 19359 S L1 AND L3
L19 1 S L16 AND L18
L20 1 S L16 AND L3
L21 12 S L1 AND L16
L22 9 DUP REM L21 (3 DUPLICATES REMOVED)

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NEWS	16	APR 28	Improved searching of U.S. Patent Classifications for U.S. patent records in CA/Caplus
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NEWS	23	JUL 01	MEDICONF removed from STN
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NEWS	25	JUL 13	SCISEARCH reloaded
NEWS	26	JUL 20	Powerful new interactive analysis and visualization software, STN AnaVist, now available
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FULL ESTIMATED COST	0.21	0.21

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FILE 'LIFESCI' ENTERED AT 12:43:44 ON 02 AUG 2005
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=> s tyrosine (a)kinase?
L1 219065 TYROSINE (A) KINASE?

=> s proto(w)oncogene
L2 117272 PROTO(W) ONCOGENE

=> s l1 and l2
L3 19359 L1 AND L2

=> s human and l3
L4 11988 HUMAN AND L3

=> s clon? or express? or recombinant
1 FILES SEARCHED...
4 FILES SEARCHED...
L5 7194083 CLON? OR EXPRESS? OR RECOMBINANT

=> s 14 and 15
L6 8010 L4 AND L5

=> s uterus or leukemia or adenocarcinoma
7 FILES SEARCHED...
L7 1361302 UTERUS OR LEUKEMIA OR ADENOCARCINOMA

=> s 16 and 17
L8 1451 L6 AND L7

=> s 18 and hippocampus
L9 5 L8 AND HIPPOCAMPUS

=> d 1-5 ibib ab

L9 ANSWER 1 OF 5 MEDLINE on STN
ACCESSION NUMBER: 96064664 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7592801
TITLE: Overexpression of the Bcl-2 protein increases the half-life of p21Bax.
AUTHOR: Miyashita T; Kitada S; Krajewski S; Horne W A; Delia D; Reed J C
CORPORATE SOURCE: La Jolla Cancer Research Foundation, California 92037, USA.
CONTRACT NUMBER: CA-60381 (NCI)
SOURCE: Journal of biological chemistry, (1995 Nov 3) 270 (44) 26049-52.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199512
ENTRY DATE: Entered STN: 19960124
Last Updated on STN: 19960124
Entered Medline: 19951221

AB Bcl-2 and Bax are homologous proteins which can heterodimerize with each other. These proteins have opposing effects on cell survival when overexpressed in cells, with Bcl-2 blocking and Bax promoting apoptosis. Here we demonstrate that gene transfer-mediated elevations in Bcl-2 protein levels result in a marked increase in the steady-state levels of endogenous p21Bax protein as determined by immunoblotting in the Jurkat T-cell and 697 pre-B-cell **leukemia** cell lines, but not in several other cell lines including CEM T-cell **leukemia**, 32D.3 myeloid progenitor, PC12 pheochromocytoma, and NIH-3T3 fibroblasts. Steady-state levels of p21Bax protein were also elevated in the lymph nodes of Bcl-2 transgenic mice in which a BCL-2 transgene is **expressed** at high levels in B-cells. Northern blot analysis of BCL-2-transfected and control-transfected Jurkat and 697 **leukemia** cells revealed no Bcl-2-induced alterations in the steady-state levels of BAX mRNAs. In contrast, L-[35S]methionine pulse-chase analysis indicated a marked increase in the half-life ($t_{1/2}$) of the p21Bax protein in BCL-2-transfected 697 cells compared to control-transfected cells ($t_{1/2}$ > 24 h versus approximately 4 h), whereas the rate of Bax degradation was unaltered in Bcl-2-transfected CEM cells. The results demonstrate that levels of the proapoptotic p21Bax protein can be post-translationally regulated by Bcl-2, probably in a tissue-specific fashion, and suggest the existence of a feedback mechanism that may help to maintain the ratio of Bcl-2 to Bax protein in physiologically appropriate ranges.

L9 ANSWER 2 OF 5 MEDLINE on STN
ACCESSION NUMBER: 95015773 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7523489
TITLE: **Expression** of c-kit and kit ligand proteins in

normal **human** tissues.
AUTHOR: Lammie A; Drobnjak M; Gerald W; Saad A; Cote R;
Cordon-Cardo C
CORPORATE SOURCE: Department of Pathology, Memorial Sloan-Kettering Cancer
Center, New York, NY 10021.
CONTRACT NUMBER: CA-47179 (NCI)
CA-47538 (NCI)
DK47650 (NIDDK)
SOURCE: journal of histochemistry and cytochemistry : official
journal of the Histochemistry Society, (1994 Nov) 42 (11)
1417-25.
Journal code: 9815334. ISSN: 0022-1554.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199411
ENTRY DATE: Entered STN: 19941222
Last Updated on STN: 20000303
Entered Medline: 19941118

AB The c-kit receptor and its cognate ligand, KL, play a critical role in melanogenesis, gametogenesis, and hematopoiesis. Studies on the **expression** of c-kit and KL have been primarily focused on mouse development. We undertook the present study to characterize the pattern of **expression** of these molecules in normal adult **human** tissues. Using immunohistochemistry and consecutive tissue sections from the same block, we evaluated a variety of well-preserved normal tissues for c-kit and KL microanatomic distribution. c-kit protein was identified in tissue mast cells, melanocytes, glandular epithelial cells of breast, parotid, dermal sweat, and esophageal glands. Scattered c-kit immunoreactivity was also observed for testicular and ovarian interstitial cells. A striking regional distribution of c-kit was detected in the central nervous system, particularly in the cerebellum, **hippocampus**, and dorsal horn of the spinal cord. KL protein was identified in cells complementary to staining for the receptor, such as glandular myoepithelium of breast and sweat glands. Intense KL immunoreactivity was observed in smooth muscle cells of the bladder, cervix, **uterus**, and gastrointestinal tract, as well as in striated and cardiac muscle. Strong KL staining was also detected in prostate fibromuscular stroma cells. In the central nervous system, KL **expression** was confined to Golgi and Purkinje cells in the cerebellum. These results suggest a role for this receptor and its ligand in the maintenance of a variety of fully differentiated tissues.

L9 ANSWER 3 OF 5 BIOTECHDS COPYRIGHT 2005 THE THOMSON CORP. on STN

ACCESSION NUMBER: 2002-07016 BIOTECHDS

TITLE: Nucleic acids encoding a **proto-oncogene tyrosine kinase**, useful for the prevention, diagnosis and treatment of e.g. **leukemia** and lung tumors;
tyrosine-kinase gene transfer by
vector **expression** in host cell for cancer gene
therapy

AUTHOR: GAN W; YE J; DI FRANCESCO V; BEASLEY E M
PATENT ASSIGNEE: PE CORP NY
PATENT INFO: US 6340584 22 Jan 2002
APPLICATION INFO: US 2001-817180 27 Mar 2001
PRIORITY INFO: US 2001-817180 27 Mar 2001
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2002-138497 [18]

AB DERWENT ABSTRACT:
NOVELTY - Isolated nucleic acid sequences (I) encoding a **proto-**

oncogene tyrosine kinase (poTK), is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following: (1) an isolated nucleic acid molecule (I) comprising a nucleotide sequence selected from: (a) a nucleotide sequence that encodes a defined 752 amino acid sequence (A1) given in the specification; (b) a nucleic acid molecule comprising a defined 2674 nucleotide sequence (N1) given in the specification; (c) a nucleic acid molecule consisting of a defined 15297 nucleotide sequence (N2) given in the specification; and (d) a nucleotide sequence that is completely complementary to a nucleotide sequence of (a)-(c); (2) a nucleic acid vector (II) comprising (I); (3) a host cell (IV) containing (III); and (4) a process (V) for producing a polypeptide comprising culturing the host cell (IV) under conditions sufficient for the production of the polypeptide, and recovering the peptide from the host cell culture.

BIOTECHNOLOGY - Preferred Nucleic Acid Molecules: (I) Comprises (N1) or (N2). Preferred Vectors: (II) Is a plasmid, virus or bacteriophage. The isolated nucleic acid molecule is inserted into the vector in proper orientation and correct reading frame so that the protein of (A1) may be **expressed** by a cell transformed with the vector. The isolated nucleic acid molecule is operatively linked to a promoter sequence. Preparation: (I) Has been isolated from **human** placenta, lung tumors, kidney tumors, pregnant **uterus**, **leukemia**, stomach **adenocarcinoma**, and **hippocampus**, via standard methodologies. The poTK it encodes may be produced by culturing (IV).

ACTIVITY - Cytostatic; Anti-leukemic. No biological data given.

MECHANISM OF ACTION - Gene therapy; Protein therapy; Vaccine; Enzymatic-inhibition; Anti-kinase.

USE - (I) and the poTK may be used in the prevention, diagnosis and treatment of diseases associated with inappropriate poTK **expression**, such as lung and kidney tumors, **leukemia** and stomach **adenocarcinoma**. For example, (I) (or (II)) and poTK may be used to treat disorders associated with decreased **expression** by rectifying mutations or deletions in a patient's genome that affect the activity of poTK by **expressing** inactive proteins or to supplement the patients own production of poTK. Additionally, (I) and (II) may be used to produce the poTK, by inserting the nucleic acid into a host cell (III) and culturing the cell to **express** the protein (V). (I) and its complementary sequences may also be used as DNA probes in diagnostic assays to detect and quantitate the presence of similar nucleic acids in samples, and therefore which patients may be in need of restorative therapy. The encoded poTK may be used as an antigen in the production of antibodies against poTK and in assays to identify modulators of poTK **expression** and activity. The anti-poTK antibodies and antagonists may be used to down regulate **expression** and activity and as diagnostic agents for detecting the presence of poTK in samples.

ADMINISTRATION - No details given. (49 pages)

L9 ANSWER 4 OF 5 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 1994:704903 SCISEARCH

THE GENUINE ARTICLE: PP282

TITLE: **EXPRESSION OF C-KIT AND KIT-LIGAND PROTEINS IN NORMAL HUMAN TISSUES**

AUTHOR: LAMMIE A (Reprint); DROBNJAK M; GERALD W; SAAD A; COTE R; CORDONCARDO C

CORPORATE SOURCE: MEM SLOAN KETTERING CANC CTR, DEPT PATHOL, NEW YORK, NY 10021; IMPATH LABS, NEW YORK, NY; UNIV SO CALIF, MED CTR, DEPT PATHOL, LOS ANGELES, CA

COUNTRY OF AUTHOR: USA

SOURCE: JOURNAL OF HISTOCHEMISTRY & CYTOCHEMISTRY, (NOV 1994) Vol. 42, No. 11, pp. 1417-1425.
ISSN: 0022-1554.

PUBLISHER: HISTOCHEMICAL SOC INC, MT SINAI MEDICAL CENTER 19 EAST
 98TH ST SUTIE 9G, NEW YORK, NY 10029.
 DOCUMENT TYPE: Article; Journal
 FILE SEGMENT: LIFE
 LANGUAGE: English
 REFERENCE COUNT: 60
 ENTRY DATE: Entered STN: 1994
 Last Updated on STN: 1994

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The c-kit receptor and its cognate ligand, KL, play a critical role in melanogenesis, gametogenesis, and hematopoiesis. Studies on the **expression** of c-kit and KL have been primarily focused on mouse development. We undertook the present study to characterize the pattern of **expression** of these molecules in normal adult **human** tissues. Using immunohistochemistry and consecutive tissue sections from the same block, we evaluated a variety of well-preserved normal tissues for c-kit and KL microanatomic distribution. c-kit protein was identified in tissue mast cells, melanocytes, glandular epithelial cells of breast, parotid, dermal sweat, and esophageal glands. Scattered c-kit immunoreactivity was also observed for testicular and ovarian interstitial cells. A striking regional distribution of c-kit was detected in the central nervous system, particularly in the cerebellum, **hippocampus**, and dorsal horn of the spinal cord. KL protein was identified in cells complementary to staining for the receptor, such as glandular myoepithelium of breast and sweat glands. Intense KL immunoreactivity was observed in smooth muscle cells of the bladder, cervix, **uterus**, and gastrointestinal tract, as well as in striated and cardiac muscle. Strong KL staining was also detected in prostate fibromuscular stroma cells. In the central nervous system, KL **expression** was confined to Golgi and Purkinje cells in the cerebellum. These results suggest a role for this receptor and its ligand in the maintenance of a variety of fully differentiated tissues.

L9 ANSWER 5 OF 5 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:66832 HCAPLUS
 DOCUMENT NUMBER: 136:113834
 TITLE: Protein, gene and cDNA sequences of **human**
 protein kinase sequence homolog
 INVENTOR(S): Gan, Weiniu; Ye, Jane; Di Francesco, Valentina;
 Beasley, Ellen M.
 PATENT ASSIGNEE(S): PE Corporation (NY), USA
 SOURCE: U.S., 50 pp.
 CODEN: USXXAM
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 2
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6340584	B1	20020122	US 2001-817180	20010327
US 2002168741	A1	20021114	US 2001-3295	20011206
US 6686187	B2	20040203		
CA 2441661	AA	20021003	CA 2002-2441661	20020327
WO 2002077191	A2	20021003	WO 2002-US9325	20020327
WO 2002077191	A3	20040311		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,

KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB,
 GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA,
 GN, GQ, GW, ML, MR, NE, SN, TD, TG
 EP 1421186 A2 20040526 EP 2002-728575 20020327
 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
 IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
 US 2004063130 A1 20040401 US 2003-660763 20030912
 PRIORITY APPLN. INFO.: US 2001-817180 A3 20010327
 US 2001-3295 A 20011206
 WO 2002-US9325 W 20020327

AB The invention provides protein and cDNA and genomic sequences for a novel human protein, which shares sequence homol. to a known protein kinase, and is related to the **proto-oncogene tyrosine kinase** subfamily. The gene is **expressed** in placenta, lung tumors, kidney tumors, pregnant **uterus, leukemia, stomach adenocarcinoma, and hippocampus**. Ten novel single nucleotide polymorphism sites (beyond the ORF or in intron regions) were identified. Thus, the present invention specifically provides isolated peptide and nucleic acid mols., methods of identifying orthologs and paralogs of the protein kinase peptides, methods of identifying modulators of the protein kinase peptides, and methods of diagnosis and treatment of diseases associated with the protein kinase.

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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 L7 1361302 S UTERUS OR LEUKEMIA OR ADENOCARCINOMA
 L8 1451 S L6 AND L7
 L9 5 S L8 AND HIPPOCAMPUS

=> s 12(w)11

L10 67 L2(W) L1

=> dup rem 110

PROCESSING COMPLETED FOR L10

L11 33 DUP REM L10 (34 DUPLICATES REMOVED)

=> d 1-33 ibib ab

L11 ANSWER 1 OF 33 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
 ACCESSION NUMBER: 2005:8491 BIOSIS
 DOCUMENT NUMBER: PREV200500004554
 TITLE: Early onset hereditary papillary renal carcinoma: Germline missense mutations in the tyrosine kinase domain of the met proto-oncogene.
 AUTHOR(S): Schmidt, Laura S. [Reprint Author]; Nickerson, Michael L.; Angeloni, Debora; Glenn, Gladys M.; Walther, McClellan M.; Albert, Paul S.; Warren, Michelle B.; Choyke, Peter L.; Torres-Cabala, Carlos A.; Merino, Maria J.; Brunet, Joan; Berez, Victoria; Borrás, Joan; Sesia, Giovanni; Middelton,

Lindsay; Phillips, John L.; Stolle, Catherine; Zbar, Berton; Pautler, Stephen E.; Linehan, W. Marston
 CORPORATE SOURCE: Immunobiol LabCanc Res Ctr, NCI, Bldg 560, Room 12-69, Frederick, MD, 21702, USA
 schmidt1@mail.ncifcrf.gov
 SOURCE: Journal of Urology, (October 2004) Vol. 172, No. 4, Part 1, pp. 1256-1261. print.
 CODEN: JOURAA. ISSN: 0022-5347.
 DOCUMENT TYPE: Article
 LANGUAGE: English
 ENTRY DATE: Entered STN: 16 Dec 2004
 Last Updated on STN: 16 Dec 2004

AB Purpose: Hereditary papillary renal carcinoma (HPRC) is characterized by a predisposition to multiple, bilateral papillary type 1 renal tumors caused by inherited activating missense mutations in the tyrosine kinase domain of the MET proto-oncogene. In the current study we evaluated the clinical phenotype and germline MET mutation of 3 new HPRC families. We describe the early onset clinical features of HPRC. Materials and Methods: We identified new HPRC families of Italian (family 177), Spanish (family 223) and Cuban (family 268) descent. We evaluated their clinical features, performed MET mutation analysis by denaturing high performance liquid chromatography and DNA sequencing, and estimated age dependent penetrance and survival using Kaplan-Meier analysis. We characterized renal tumors by histology and fluorescence in situ hybridization. Results: Identical germline MET c.3522GfwdarwA mutations (V11101) were identified in families 177 and 268 but no evidence of a founder effect was found. Affected members of family 223 carried a germline c.3906GfwdarwC.3522GfwdarwA MET mutation (V12381). Age dependent penetrance but not survival was significantly earlier for the c.3522GfwdarwA mutation than for the c.3906GfwdarwA mutation in these HPRC families. Trisomy of chromosome 7 and papillary renal carcinoma type 1 histology were detected in papillary renal tumors. Conclusions: HPRC can occur in an early onset form. The median age for renal tumor development in these 3 HPRC families was 46 to 63 years. HPRC associated papillary renal tumors may be aggressive and metastasize, leading to mortality. Median survival age was 60 to 70 years. Families with identical germline mutations in MET do not always share a common ancestor. HPRC is characterized by germline mutations in MET and papillary type 1 renal tumor histology.

L11 ANSWER 2 OF 33 MEDLINE on STN DUPLICATE 1
 ACCESSION NUMBER: 2004511210 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 15370560
 TITLE: Proteomic analysis of cholesteatoma.
 AUTHOR: Kim Jeong Lim; Jung Hak Hyun
 CORPORATE SOURCE: Department of Biomedical Sciences, Korea University College of Medicine, Seoul.
 SOURCE: Acta oto-laryngologica, (2004 Sep) 124 (7) 783-8.
 Journal code: 0370354. ISSN: 0001-6489.
 PUB. COUNTRY: Norway
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200501
 ENTRY DATE: Entered STN: 20041015
 Last Updated on STN: 20050105
 Entered Medline: 20050104

AB OBJECTIVE: Proteomic analysis with 2D electrophoresis and matrix-assisted laser desorption and ionization time-of-flight mass spectrometry (MALDI-TOF MS) may be a powerful tool for identifying and characterizing the specific proteins relating to the pathogenesis of some diseases, including cholesteatoma. The purpose of this study was to identify upregulated proteins in human cholesteatoma in comparison with canal skin using proteomic analysis. MATERIAL AND METHODS: Three cholesteatoma

matrices and three samples of normal retroauricular skin were obtained intraoperatively from cholesteatoma patients. We performed 2D electrophoresis in order to separate the proteins by molecular weight and approximately detected 600 protein spots. We then analyzed the 17 upregulated spots from the cholesteatoma matrices using MALDI-TOF MS. Upregulation of proliferating cell nuclear antigen (PCNA) and osteoclast stimulating factor-1 (OSF-1), two candidate proteins in the pathogenesis of cholesteatoma, was confirmed by means of immunohistochemistry and reverse transcriptase polymerase chain reaction. RESULTS: Interestingly, two candidate proteins, PCNA and OSF-1, relating to cellular proliferation and bone destruction were identified in the cholesteatoma matrices and we also detected nine proteins relating to the mechanism of signal transduction in the pathogenesis of cholesteatoma, including P-13-kinase P55 gamma subunit, RET **proto-oncogene tyrosine kinase** receptor and adenosine kinase. CONCLUSION: Proteomic analysis may be a powerful tool for the identification and characterization of many promising candidate proteins relating to cholesteatoma.

L11 ANSWER 3 OF 33 BIOTECHDS COPYRIGHT 2005 THE THOMSON CORP. on STN
ACCESSION NUMBER: 2003-22614 BIOTECHDS

TITLE: C-src tyrosine kinase activity is associated with tumor colonization in bone and lung in an animal model of human breast cancer metastasis;

proto-oncogene tyrosine-kinase and vector expression in cell culture for use as a drug target in disease therapy

AUTHOR: MYOUI A; NISHIMURA R; WILLIAMS PJ; HIRAGA T; TAMURA D; MICHIGAMI T; MUNDY GR; YONEDA T

CORPORATE SOURCE: Univ Texas; Osaka Univ; Osaka Univ; Osaka Med Ctr; Inst Mat and Child Hlth

LOCATION: Yoneda T, Univ Texas, Hlth Sci Ctr, Dept Med, Div Endocrinol and Metab, 7703 Floyd Curl Dr, San Antonio, TX 78229 USA

SOURCE: CANCER RESEARCH; (2003) 63, 16, 5028-5033
ISSN: 0008-5472

DOCUMENT TYPE: Journal

LANGUAGE: English

AB AUTHOR ABSTRACT - The proto-oncogene, c-src, has been implicated in the tumorigenesis in breast cancer. However, the relationship of c-src with distant metastasis is unclear. Moreover, the role of c-src in organ-preferential metastasis of breast cancer is unknown. Because breast cancer has a strong predilection for metastasizing to bone, we examined the role of c-src in bone metastases using an animal model in which inoculation of the MDA-231 human breast cancer cells into the left cardiac ventricle preferentially developed osteolytic bone metastases in female nude mice. A clone of the MDA-231 with the increased capacity of bone metastasis exhibited elevated c-src tyrosine kinase (TK) activity compared with parental cells. MDAsrc527 cells caused significantly increased size of the osteolytic bone metastases with increased number of osteoclasts and mitotic cancer cells compared with MDA-231EV or MDAsrcWT. In contrast, MDAsrc295 cells caused impaired metastases to bone. Of note, mice inoculated with MDAsrc295 cells via tail vein developed reduced lung metastases and prolonged survival compared with mice with MDA-231EV cells, suggesting that c-src TK is unlikely to play a specific role in bone metastases. The growth in vitro and in vivo and production of parathyroid hormone-related protein, a key cytokine in the pathogenesis of osteolytic bone metastases in breast cancer, were promoted in MDAsrc527 and diminished in MDAsrc295. These results suggest that c-src TK is associated with the capacity of breast cancer to metastasize to bone through regulating cell growth and parathyroid hormone-related protein production. Our results together with the fact that c-src is an essential molecule for bone resorption by osteoclasts, which are central players in osteolytic bone metastases, support the notion that c-src TK

is a potential target molecule for designing novel therapeutic interventions, especially for bone metastases in breast cancer. (6 pages)

L11 ANSWER 4 OF 33 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2004:152343 BIOSIS
DOCUMENT NUMBER: PREV200400147834
TITLE: Exploring transcriptome alterations in multiple myeloma by high density oligonucleotide microarray: A comparative analysis with polyclonal plasmablasts.
AUTHOR(S): De Vos, John [Reprint Author]; Reme, Thierry; Tarte, Karin; Pantesco, Veronique; Rossi, Jean-Francois; Klein, Bernard [Reprint Author]
CORPORATE SOURCE: Unit for Cellular Therapy, CHU, Montpellier, France
SOURCE: Blood, (November 16 2003) Vol. 102, No. 11, pp. 678a-679a. print.
Meeting Info.: 45th Annual Meeting of the American Society of Hematology. San Diego, CA, USA. December 06-09, 2003. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; (Meeting Poster)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 17 Mar 2004
Last Updated on STN: 17 Mar 2004

AB Microarrays provide the unique possibility to analyze the expression alteration of thousands of different genes and are therefore an adequate tool to explore the complex deregulation of plasma cell homeostasis in multiple myeloma (MM). We compared the RNA level of 12625 genes between 11 myeloma samples (7 highly purified primary myeloma samples and 5 human myeloma cell lines) and 6 highly purified plasmablastic cell (PPC) samples obtained by in vitro differentiation of peripheral blood B cells from normal donors using Affymetrix U95Av2 oligonucleotide microarrays. Two unsupervised clustering algorithms classified these 18 samples into two distinct clusters: a malignant plasma cell cluster and a normal plasma cell cluster. Two hundred thirty eight genes were significantly ($P < 0.05$) up-regulated (ratio > 2.5) in MM samples whereas 142 were down-regulated (ratio < 0.4). Among the genes overexpressed in malignant plasma cells, 42 (18%) were coding for transmembrane proteins and 18 (8%) were coding for secreted proteins. These included members of the Frizzled family such as FRZB, FZB6, WNT5A, members of the TGF- α superfamily such as BMP6, activin A receptor, type II and SMAD1, complement genes or functionally related genes such as C1R, C4A and CD46, other growth factors or growth factors receptors such as midkine (MDK), adrenomedulin (ADM), VEGF, the c-met **proto-oncogene tyrosine kinase** and IGF1R, and the tetraspanins CD9, CD151 and TSPAN-3. Some of these genes were already known to be involved in the biology of malignant plasma cells whereas others are new to our knowledge. These expression data on genes coding for transmembrane and secreted proteins not only provide a new insight into the understanding of myeloma disease but may also highlight new potential therapeutic targets for monoclonal antibody targeted interventions. In order to extend these findings on a genome wide scale, we are currently hybridizing malignant and normal plasma cell samples on Affymetrix U133 A and B chips analyzing the expression of circa 33 000 different transcripts.

L11 ANSWER 5 OF 33 BIOTECHDS COPYRIGHT 2005 THE THOMSON CORP. on STN
DUPLICATE 2
ACCESSION NUMBER: 2002-07016 BIOTECHDS
TITLE: Nucleic acids encoding a **proto-oncogene tyrosine kinase**, useful for the prevention, diagnosis and treatment of e.g. leukemia and lung tumors; tyrosine-kinase gene transfer by vector expression in host

cell for cancer gene therapy

AUTHOR: GAN W; YE J; DI FRANCESCO V; BEASLEY E M
PATENT ASSIGNEE: PE CORP NY
PATENT INFO: US 6340584 22 Jan 2002
APPLICATION INFO: US 2001-817180 27 Mar 2001
PRIORITY INFO: US 2001-817180 27 Mar 2001
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2002-138497 [18]

AB DERWENT ABSTRACT:

NOVELTY - Isolated nucleic acid sequences (I) encoding a **proto-oncogene tyrosine kinase** (poTK), is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following: (1) an isolated nucleic acid molecule (I) comprising a nucleotide sequence selected from: (a) a nucleotide sequence that encodes a defined 752 amino acid sequence (A1) given in the specification; (b) a nucleic acid molecule comprising a defined 2674 nucleotide sequence (N1) given in the specification; (c) a nucleic acid molecule consisting of a defined 15297 nucleotide sequence (N2) given in the specification; and (d) a nucleotide sequence that is completely complementary to a nucleotide sequence of (a)-(c); (2) a nucleic acid vector (II) comprising (I); (3) a host cell (IV) containing (III); and (4) a process (V) for producing a polypeptide comprising culturing the host cell (IV) under conditions sufficient for the production of the polypeptide, and recovering the peptide from the host cell culture.

BIOTECHNOLOGY - Preferred Nucleic Acid Molecules: (I) Comprises (N1) or (N2). Preferred Vectors: (II) Is a plasmid, virus or bacteriophage. The isolated nucleic acid molecule is inserted into the vector in proper orientation and correct reading frame so that the protein of (A1) may be expressed by a cell transformed with the vector. The isolated nucleic acid molecule is operatively linked to a promoter sequence. Preparation: (I) Has been isolated from human placenta, lung tumors, kidney tumors, pregnant uterus, leukemia, stomach adenocarcinoma, and hippocampus, via standard methodologies. The poTK it encodes may be produced by culturing (IV).

ACTIVITY - Cytostatic; Anti-leukemic. No biological data given.

MECHANISM OF ACTION - Gene therapy; Protein therapy; Vaccine; Enzymatic-inhibition; Anti-kinase.

USE - (I) and the poTK may be used in the prevention, diagnosis and treatment of diseases associated with inappropriate poTK expression, such as lung and kidney tumors, leukemia and stomach adenocarcinoma. For example, (I) (or (II)) and poTK may be used to treat disorders associated with decreased expression by rectifying mutations or deletions in a patient's genome that affect the activity of poTK by expressing inactive proteins or to supplement the patients own production of poTK. Additionally, (I) and (II) may be used to produce the poTK, by inserting the nucleic acid into a host cell (III) and culturing the cell to express the protein (V). (I) and its complementary sequences may also be used as DNA probes in diagnostic assays to detect and quantitate the presence of similar nucleic acids in samples, and therefore which patients may be in need of restorative therapy. The encoded poTK may be used as an antigen in the production of antibodies against poTK and in assays to identify modulators of poTK expression and activity. The anti-poTK antibodies and antagonists may be used to down regulate expression and activity and as diagnostic agents for detecting the presence of poTK in samples.

ADMINISTRATION - No details given. (49 pages)

L11 ANSWER 6 OF 33 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2003:356309 BIOSIS
DOCUMENT NUMBER: PREV200300356309
TITLE: The Molecular Basis of the Transition of MGUS to Multiple Myeloma.
AUTHOR(S): Davies, Faith E. [Reprint Author]; Dring, Ann M.; Li,

Cheng; Rawstron, Andrew C.; Shamma, Masood; Hideshima, Teru; Chauhan, Dharminder; Tai, Isabella T.; Auclair, Daniel; Robinson, Elizabeth; Wong, Wing H.; Munshi, Nikhil C.; Morgan, Gareth J.; Anderson, Kenneth C. [Reprint Author]

CORPORATE SOURCE: Academic Department of Haematology and Oncology, University of Leeds, Leeds, West Yorkshire, UK

SOURCE: Blood, (November 16 2002) Vol. 100, No. 11, pp. Abstract No. 377. print.

Meeting Info.: 44th Annual Meeting of the American Society of Hematology. Philadelphia, PA, USA. December 06-10, 2002. American Society of Hematology.

CODEN: BLOOAW. ISSN: 0006-4971.

DOCUMENT TYPE: Conference; (Meeting)

Conference; Abstract; (Meeting Abstract)

LANGUAGE: English

ENTRY DATE: Entered STN: 6 Aug 2003

Last Updated on STN: 6 Aug 2003

AB MGUS can be considered a premalignant phase of myeloma (MM) and MGUS plasma cells (PCs) although distinct in their clinical behavior are clearly related to MM PCs. Understanding the molecular basis of the transition from MGUS to MM can provide considerable insight into the multi-step pathogenesis of MM. This transition has been studied using cytogenetics and mutational analysis however consistent changes suitable for the further investigation have not been identified. Expression based analysis can highlight genes and gene families important in this transition which may be potential future therapeutic targets. We have analyzed PCs from 5 normals (N), 5 MGUS and 31 MM following CD138+ selection using the Affymetrix U95Av2 gene chip comparing 10,000 known expressed sequences. DCHIP was used to hierarchically cluster and compare the resultant data sets. 421 genes separated N PCs from MM PCs, whereas 287 genes separated N PCs from MGUS PCs. Interestingly the majority of genes were down-regulated (28 upregulated, 393 downregulated). The data sets were validated by comparing genes already highlighted as being important in differentiating N and malignant PCs using flow cytometry and RT-PCR. These genes included the downregulation of CD38, CD70, CCR2, VCAM1, MRC1, SDF1 and PF4. The transition of MGUS to MM was more closely examined and using the same strict analysis criteria the number of genes separating MGUS and MM was considerably less (28 genes), than those separating N and malignant PCs suggesting that MGUS PCs are more like MM PCs than N PCs, with only a limited set of genes being differentially regulated. The underlying basis of these changes may be understood more clearly by looking at the functional classes of genes that are altered. Important genes in the N vs Malignant comparison are transcription factors - XBP1, YY1, CBF and seven - absentia; cell cycle genes - CDC like kinase 1, protein phosphatase 2, ring finger protein 24, and selenoprotein P; signal transduction genes - CD163, small inducible cytokine subfamily C and CDK2 associated protein 2; cell death genes - MAD3 and beclin 1; oncogenes - c-myc, sub 1.5mRNA and LAF4; and tumor suppressor genes - DOCl, Rb1 and disabled. In comparison the genes differentiating MGUS from MM are more limited but include a number of potentially important genes affecting cell growth and maintenance - defensin, protein kinase C substrate, CD85, cathepsin G, s100 calcium binding protein A8, glutamine synthase, and CD27; signal transduction - MD2 protein, c-mer **proto-oncogene tyrosine kinase**, Fc fragment of IgE and LIM and SH3 protein 1; structural proteins - pro-platelet basic protein, actinin, adducin 1 and vinculin; and developmental processes - ring finger protein 1, and thymosin. Interestingly no genes involved in apoptosis were highlighted as being differentially expressed between MGUS and MM. Validation experiments using RT-PCR, flow cytometry and protein expression are underway. In conclusion gene array analysis highlights the differences in gene expression levels between N PCs, MGUS PCs and MM PCs and supports the multi-step pathogenesis of MM. A large list of genes

differentiates N PCs from malignant PCs (MGUS+MM) whereas the number of differentially expressed genes between MGUS PCs and MM PCs is small. Further investigation of the MGUS vs MM gene list is warranted as these genes maybe potential therapeutic targets.

L11 ANSWER 7 OF 33 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2001405032 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11443173
TITLE: Novel patterns of gene expression in pituitary adenomas identified by complementary deoxyribonucleic acid microarrays and quantitative reverse transcription-polymerase chain reaction.
AUTHOR: Evans C O; Young A N; Brown M R; Brat D J; Parks J S; Neish A S; Oyesiku N M
CORPORATE SOURCE: Department of Neurosurgery and Laboratory of Molecular Neurosurgery and Biotechnology, Emory University School of Medicine, Atlanta, Georgia 30322, USA.
SOURCE: Journal of clinical endocrinology and metabolism, (2001 Jul) 86 (7) 3097-107.
Journal code: 0375362. ISSN: 0021-972X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 20010806
Last Updated on STN: 20010806
Entered Medline: 20010802

AB Pituitary adenomas account for approximately 10% of intracranial tumors, but little is known of the oncogenesis of these tumors. The identification of tumor-specific genes may further elucidate the pathways of tumor formation. We used complementary DNA microarrays to examine gene expression profiles in nonfunctioning, PRL, GH, and ACTH secreting adenomas, compared with normal pituitary. Microarray analysis showed that 128 of 7075 genes examined were differentially expressed. We then analyzed three genes with unique expression patterns and oncogenic importance by RT-real time quantitative PCR in 37 pituitaries. Folate receptor gene was significantly overexpressed in nonfunctioning adenomas but was significantly underexpressed in PRL and GH adenomas, compared with controls and to other tumors. The ornithine decarboxylase gene was significantly overexpressed in GH adenomas, compared with other tumor subtypes but was significantly underexpressed in ACTH adenomas. C-met **proto-oncogene tyrosine kinase** gene was significantly overexpressed in ACTH adenomas but was significantly underexpressed in PRL adenomas. We have shown that at least three genes involved in carcinogenesis in other tissues are also aberrantly regulated in the major types of pituitary tumors. The evaluation of candidate genes that emerge from these experiments provides a rational approach to investigate those genes significant in tumorigenesis.

L11 ANSWER 8 OF 33 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2001:230318 BIOSIS
DOCUMENT NUMBER: PREV200100230318
TITLE: A homozygous missense mutation in the tyrosine kinase domain of the RET proto-oncogene in an infant with total intestinal aganglionosis.
AUTHOR(S): Shimotake, Takashi [Reprint author]; Go, Seitetsu; Inoue, Kyoko; Tomiyama, Hideki; Iwai, Naomi
CORPORATE SOURCE: Division of Surgery, Children's Research Hospital, Kyoto Prefectural University of Medicine, 465
Kawaramachi-Hirokoji, Kamigyo-ku, Kyoto, 602-0841, Japan
SOURCE: American Journal of Gastroenterology, (April, 2001) Vol. 96, No. 4, pp. 1286-1291. print.

CODEN: AJGAAR. ISSN: 0002-9270.

DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 16 May 2001
Last Updated on STN: 18 Feb 2002

AB Germline mutations of the RET proto-oncogene (RET), its ligand glial cell-derived neurotrophic factor (GDNF), and neurturin (NTN) gene have been reported in patients with Hirschsprung's disease. A targeted mutation in the tyrosine kinase domain of RET produced total intestinal aganglionosis and renal agenesis in homozygous transgenic mice. Here we describe a homozygous mutation of the human gene for the RET tyrosine kinase domain that was present in a male neonate with total intestinal aganglionosis. Gut wall biopsy specimens from the stomach to the anorectum showed no ganglion cells. No urinary tract abnormalities were detected. Genomic DNAs were isolated from peripheral blood lymphocytes of the infant and his parents. DNA sequences of all the RET/GDNF/NTN coding regions were determined using a direct DyeDeoxy Terminator Cycle method. A homozygous missense mutation (CGG-to-TGG) at RET codon 969 was identified in this patient, which resulted in an amino acid change from arginine to tryptophan. No germline RET/GDNF/NTN mutations were found in his parents. In this case, the homozygous RET mutation seemed to cause a critical alteration of the Ret tyrosine kinase activity, which resulted in total intestinal aganglionosis but not renal agenesis. Discrepancies in phenotypic expression between humans and mice suggest differing threshold values for RET signal transduction in species or organs.

L11 ANSWER 9 OF 33 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 2001:314188 BIOSIS

DOCUMENT NUMBER: PREV200100314188

TITLE: Structural basis of oncogenic activation caused by point mutations in the kinase domain of the MET proto-oncogene: Modeling studies.

AUTHOR(S): Miller, Maria [Reprint author]; Ginalska, Krzysztof; Lesyng, Bogdan; Nakaigawa, Noboru; Schmidt, Laura; Zbar, Berton

CORPORATE SOURCE: Macromolecular Crystallography Laboratory, NCI at Frederick, Frederick, MD, 21702, USA
millerm@ncifcrf.gov

SOURCE: Proteins, (July 1, 2001) Vol. 44, No. 1, pp. 32-43. print.
CODEN: PSFGEY. ISSN: 0887-3585.

DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 4 Jul 2001
Last Updated on STN: 19 Feb 2002

AB Missense mutations in the tyrosine kinase domain of the MET proto-oncogene occur in selected cases of papillary renal carcinoma. In biochemical and biological assays, these mutations produced constitutive activation of the MET kinase and led to tumor formation in nude mice. Some mutations caused transformation of NIH 3T3 cells. To elucidate the mechanism of ligand-independent MET kinase activation by point mutations, we constructed several 3D models of the wild-type and mutated MET catalytic core domains. Analysis of these structures showed that some mutations (e.g., V1110I, Y1248H/D/C, M1268T) directly alter contacts between residues from the activation loop in its inhibitory conformation and those from the main body of the catalytic domain; others (e.g., M1149T, L1213V) increase flexibility at the critical points of the tertiary structure and facilitate subdomain movements. Mutation D1246N plays a role in stabilizing the active form of the enzyme. Mutation M1268T affects the S+1 and S+3 substrate-binding pockets. Models implicate that although these changes do not compromise the affinity toward the C-terminal autophosphorylation site of the MET protein, they allow for binding of the substrate for the c-Abl tyrosine kinase. We provide biochemical data supporting this observation. Mutation L1213V affects the conformation of

Tyrl212 in the active form of MET. Several somatic mutations are clustered at the surface of the catalytic domain in close vicinity of the probable location of the MET C-terminal docking site for cytoplasmic effectors.

L11 ANSWER 10 OF 33 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 2000:351189 BIOSIS
DOCUMENT NUMBER: PREV200000351189
TITLE: RET proto-oncogene mutations in thyroid carcinomas: Clinical relevance.
AUTHOR(S): Pacini, F. [Reprint author]; Elisei, R.; Romei, C.; Pinchera, A.
CORPORATE SOURCE: Dipartimento di Endocrinologia, Via Paradisa 2, 56128, Pisa, Italy
SOURCE: Journal of Endocrinological Investigation, (May, 2000) Vol. 23, No. 5, pp. 328-338. print.
CODEN: JEIND7. ISSN: 0391-4097.
DOCUMENT TYPE: Article
General Review; (Literature Review)
LANGUAGE: English
ENTRY DATE: Entered STN: 16 Aug 2000
Last Updated on STN: 8 Jan 2002

AB Different forms of RET mutations are found in papillary and medullary thyroid carcinomas. Rearrangements with other genes (RET/PTC oncogene) play a causative role in a significant proportion of papillary thyroid carcinomas. In this case, several factors influence the frequency and the type of RET/PTC, such as exposure to radiation, age and histological variant of the papillary tumor. On the other hand, the presence of the mutation does not seem to influence the biological behavior of the tumor or its response to conventional treatment modalities. In the setting of medullary thyroid cancer, germline RET point-mutations are implicated in the pathogenesis of virtually all hereditary forms and somatic point-mutations in nearly half of the sporadic forms. The clinical impact of this finding is that family members at-risk of hereditary MTC may be screened by genetic analysis, to distinguish those carrying or not-carrying the mutation. The last can be reassured on their status and relieved from further follow-up. Those with the mutation may be treated at a pre-clinical stage of the disease or even before the disease is started. The present review is focused on the clinical implication of RET gene mutations in thyroid cancer patients.

L11 ANSWER 11 OF 33 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 2001:47198 BIOSIS
DOCUMENT NUMBER: PREV200100047198
TITLE: DNA microarray analysis of HER-2/NEU regulated genes in mouse mammary carcinoma cells.
AUTHOR(S): Astolfi, A. [Reprint author]; Landuzzi, L. [Reprint author]; Ricci, C. [Reprint author]; Nicoletti, G. [Reprint author]; Rossi, I. [Reprint author]; De Giovanni, C. [Reprint author]; Lollini, P.-L. [Reprint author]; Nanni, P. [Reprint author]
CORPORATE SOURCE: Institute for Cancer Research, University of Bologna, Bologna, Italy
SOURCE: Tumori, (July-August, 2000) Vol. 86, No. 4 Suppl. 1, pp. 27. print.
Meeting Info.: XV Congress of the Italian Cancer Society. Turin, Italy. October 05-07, 2000. Italian Cancer Society.
CODEN: TUMOAB. ISSN: 0300-8916.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English

ENTRY DATE: Entered STN: 17 Jan 2001
Last Updated on STN: 12 Feb 2002

L11 ANSWER 12 OF 33 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 1999152364 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10026255
TITLE: Functional proteomics analysis of signal transduction pathways of the platelet-derived growth factor beta receptor.
AUTHOR: Soskic V; Gorlach M; Poznanovic S; Boehmer F D; Godovac-Zimmermann J
CORPORATE SOURCE: Institute for Molecular Biotechnology, Jena, Germany.
SOURCE: Biochemistry, (1999 Feb 9) 38 (6) 1757-64.
Journal code: 0370623. ISSN: 0006-2960.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199903
ENTRY DATE: Entered STN: 19990316
Last Updated on STN: 20000303
Entered Medline: 19990304

AB We report efficient methods for using functional proteomics to study signal transduction pathways in mouse fibroblasts following stimulation with PDGF. After stimulation, complete cellular proteins were separated using two-dimensional electrophoresis and phosphorylated proteins were detected with anti-phosphotyrosine and anti-phosphoserine antibodies. About 260 and 300 phosphorylated proteins were detected with the anti-phosphotyrosine and anti-phosphoserine antibodies, respectively, at least 100 of which showed prominent changes in phosphorylation as a function of time after stimulation. Proteins showing major time-dependent changes in phosphorylation were subjected to in-gel digestion with trypsin and identified by mass spectroscopy using MALDI-TOF mass fingerprinting and ESI peptide sequencing. We have observed phosphorylated proteins known to be part of the PDGF signal transduction pathway such as ERK 1, serine/threonine protein kinase akt and protein tyrosine phosphatase syp, proteins such as **proto-oncogene tyrosine kinase** fgr previously known to participate in other signal transduction pathways, and some proteins such as plexin-like protein with no previously known function in signal transduction. Information about the phosphorylation site was obtained for **proto-oncogene tyrosine kinase** fgr and for cardiac alpha-actin. The methods used here have proven to be suitable for the identification of time-dependent changes in large numbers of proteins involved in signal transduction pathways.

L11 ANSWER 13 OF 33 MEDLINE on STN DUPLICATE 5
ACCESSION NUMBER: 1998141129 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9490301
TITLE: Cloning and tissue expression of cDNAs from chromosome 5q21-22 which is frequently deleted in advanced lung cancer.
AUTHOR: Ueno K; Kumagai T; Kijima T; Kishimoto T; Hosoe S
CORPORATE SOURCE: Department of Medicine III, Osaka University Medical School, Suita, Japan.
SOURCE: Human genetics, (1998 Jan) 102 (1) 63-8.
Journal code: 7613873. ISSN: 0340-6717.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AB002437; GENBANK-AB002438; GENBANK-AB002439; GENBANK-AB002440; GENBANK-AB002441; GENBANK-AB002442;

GENBANK-AB002443; GENBANK-AB002444; GENBANK-AB002445;
GENBANK-AB002446; GENBANK-AB002447; GENBANK-AB002448;
GENBANK-AB002449; GENBANK-AB002450; GENBANK-AB002451;
GENBANK-AB002452; GENBANK-AB002453

ENTRY MONTH: 199803
ENTRY DATE: Entered STN: 19980312
Last Updated on STN: 19980312
Entered Medline: 19980303

AB Previously, we have reported that the inactivation of putative tumor-suppressor gene(s) on chromosome 5q21-22 may play an important role in the progression of lung cancer. Here, we describe the establishment of a yeast artificial chromosome (YAC) contig that spans 8-10 Mb at the 5q21-22 region. Six cosmid contigs have also been established in this YAC contig. About 35 exon-like fragments have been detected by exon-amplification, direct screening, cross-species hybridization, and searches of a database. Thus far, 14 cDNAs have been isolated, and two of them coincide with known genes, viz., cysteine dioxygenase I and geranylgeranyltransferase I. The other 12 cDNAs are considered to be novel genes. Two of these novel cDNA show partial homology to known genes, viz., semaphorin CD100 and the 28S rRNA gene. In addition, four known genes, including APC (adenomatous polyposis coli), MCC (mutated in colorectal cancer), **proto-oncogene tyrosine kinase** FER, and genomic imprinted gene U2AF1-RS1, have also been mapped in this contig. This large contig and expression map should prove crucial in the identification of susceptibility gene(s) related to the progression of lung cancer.

L11 ANSWER 14 OF 33 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN DUPLICATE 6

ACCESSION NUMBER: 96358305 EMBASE
DOCUMENT NUMBER: 1996358305
TITLE: Gene expression of neuropeptide Y and neuropeptide-Y1 receptor in relation to **proto-oncogene tyrosine kinase** A, nerve-growth-factor low-affinity-receptor and the transcription factor N-myc in human neuroblastomas.
AUTHOR: Hanze J.; Christiansen H.; Schuler D.; Worgall S.; Lampert F.; Rascher W.
CORPORATE SOURCE: Zentrum fur Kinderheilkunde, Justus-Liebig-Universitat, Feulgenstr. 12,35385 Giessen, Germany
SOURCE: International Journal of Oncology, (1996) Vol. 9, No. 6, pp. 1183-1187.
ISSN: 1019-6439 CODEN: IJONES
COUNTRY: Greece
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
007 Pediatrics and Pediatric Surgery
008 Neurology and Neurosurgery
016 Cancer
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 970214
Last Updated on STN: 970214

AB The expression of neuropeptide Y (NPY) and NPY-Y1 receptor (NPY-Y1R) in relation to that of tyrosine kinase A (trkA), nerve-growth-factor low-affinity-receptor (LNGFR) and the transcription factor N-myc was studied in 26 neuroblastomas and one ganglioneuroma by quantitative Northern-blot analysis. A correlation of NPY-Y1R with LNGFR ($r = 0.85$, $p < 0.01$) and trkA ($r = 0.38$, $p < 0.05$), respectively, could be shown, while no correlation between NPY and its receptor NPY-Y1R was observed. Comparison of a high and a low level NPY expressing group revealed that the high NPY expressing group also had high LNGFR and high trkA levels while the low NPY expressing group had low LNGFR and low trkA levels which

were significantly different (NPY: $p = 0.035$, trkA: $p = 0.008$, LNGFR $p = 0.004$). Dividing the tumors in a high and a low N-myc expressing group showed that the low N-myc expressing group contained both high and low trkA expressing tumors while the high N-myc expressing group exclusively were low level trkA expressing tumors. The frequency distribution in both groups concerning trkA expression showed a significant difference ($p < 0.01$). In conclusion the coexpression of NPY-Y1R and LNGFR or trkA may indicate a similar gene regulation during ontogenesis of the peripheral nervous system.

L11 ANSWER 15 OF 33 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1996:174698 HCAPLUS

DOCUMENT NUMBER: 124:257051

TITLE: A mutation in the RET proto-oncogene in Hirschsprung's disease affects the tyrosine kinase activity associated with multiple endocrine neoplasia type 2A and 2B

AUTHOR(S): Cosma, Maria Pia; Panariello, Luigi; Quadro, Loredana; Dathan, Nina A.; Fattoruso, Olimpia; Colantuoni, Vittorio

CORPORATE SOURCE: Dipartimento di Biochimica e Biotecnologie Mediche, CEINGE, Naples, Italy

SOURCE: Biochemical Journal (1996), 314(2), 397-400

CODEN: BIJOAK; ISSN: 0264-6021

PUBLISHER: Portland Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The authors demonstrate that a Hirschsprung (HSCR) mutation in the tyrosine kinase domain of the RET proto-oncogene abolishes in cis the tyrosine-phosphorylation associated with the activating mutation in multiple endocrine neoplasia type 2A (MEN2A) in transiently transfected Cos cells. Yet the double mutant RET2AHS retains the ability to form stable dimers, thus dissociating the dimerization from the phosphorylation potential. Co-transfection expts. with single and double mutants carrying plasmids RET2A and RET2AHS in different ratios drastically reduced the phosphorylation levels of the RET2A protein, suggesting a dominant-neg. effect of the HSCR mutation. Also, the phosphorylation associated with the multiple endocrine neoplasia type 2B (MEN2BN) allele was affected in expts. with single and double mutants carrying plasmids co-transfected under the same conditions. Finally, anal. of the enzymic activity of MEN2A and MEN2B tumors confirmed the relative levels of tyrosine phosphorylation observed in Cos cells, indicating that this condition, in vivo, may account for the RET transforming potential.

L11 ANSWER 16 OF 33 MEDLINE on STN

DUPLICATE 7

ACCESSION NUMBER: 96024081 MEDLINE

DOCUMENT NUMBER: PubMed ID: 7564919

TITLE: Synergistic induction of phospholipid metabolism by granulocyte-macrophage colony stimulating factor and steel factor in human growth factor-dependent cell line, M07e.

AUTHOR: Mantel C; Luo Z; Broxmeyer H E

CORPORATE SOURCE: Department of Medicine (Hematology/Oncology), Indiana University School of Medicine, Indianapolis 46202-5121, USA.

CONTRACT NUMBER: R01 HL46549 (NHLBI)

R01 HL49202 (NHLBI)

R37 CA36464 (NCI)

SOURCE: Lipids, (1995 Jul) 30 (7) 641-7.
Journal code: 0060450. ISSN: 0024-4201.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199511
ENTRY DATE: Entered STN: 19951227
Last Updated on STN: 19980206
Entered Medline: 19951102

AB Steel factor (SLF), the ligand for the c-kit **proto-oncogene tyrosine kinase** receptor, synergizes with several hematopoietic growth factors to produce greatly enhanced proliferation of normal human hematopoietic progenitor cells as well as that of the human growth factor-dependent myeloid cell line, M07e. The mechanisms of this phenomenon remain unknown. In an attempt to understand the cellular processes relevant to this phenomenon, we examined the effects of SLF and granulocyte-macrophage colony-stimulating factor (GM-CSF) on induced lipid metabolism in M07e cells. We find that both GM-CSF and SLF induced increased phosphatidylcholine (PC) turnover rates (biosynthesis and degradation) as measured by increased [3H]-choline labelling, with SLF being more potent than GM-CSF after 6 h of stimulation, but equipotent at 24 h of stimulation. The labelling of aqueous intermediates of PC metabolism was also increased by cytokine stimulation, most notably phosphocholine. Simultaneous stimulation with GM-CSF plus SLF resulted in a true synergistic induction of PC, lysoPC, and phosphocholine labelling. GM-CSF and SLF each induced asymmetric labelling of various phospholipid classes as measured by incorporation of different [3H]-fatty acids. [3H]-myristic acid labelling of phosphatidylserine was most prominently induced (approximately 12-fold). Cytosolic choline kinase activity was also upregulated more than twofold over control by SLF, which might contribute to the increased phosphocholine labelling. These effects may have relevance to the intracellular mechanisms of the synergistic proliferative stimulation of SLF plus GM-CSF on M07e cells.

L11 ANSWER 17 OF 33 MEDLINE on STN DUPLICATE 8
ACCESSION NUMBER: 95048120 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7959586
TITLE: A study on Fgr expression and its associated molecules in murine lymphoid and haematopoietic tissues.
AUTHOR: Hatakeyama S
CORPORATE SOURCE: Section of Pathology, Hokkaido University, Sapporo, Japan.
SOURCE: [Hokkaido igaku zasshi] Hokkaido journal of medical science, (1994 Jul) 69 (4) 669-85.
Journal code: 17410290R. ISSN: 0367-6102.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Japanese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199412
ENTRY DATE: Entered STN: 19950110
Last Updated on STN: 19950110
Entered Medline: 19941228

AB The c-fgr gene is a member of the src family of **proto-oncogene tyrosine kinases**. A monoclonal antibody (2H2 mAb) which recognizes the unique N-terminal domain of the murine c-fgr gene product (Fgr) has been established. Immune complex kinase assay with a monocytic leukemia cell line demonstrated that 2H2 precipitated a 59 kilodalton (kDa) protein, which corresponds to the molecular weight of murine Fgr. Fgr was expressed highly in lymph nodes, slightly in spleen and peripheral blood leukocytes and barely in thymus. The Fgr was hardly detectable in bone marrow. Immunohistochemical analysis showed that the expression of Fgr was restricted to cells of monocyte/macrophage lineage located in the marginal zone of the spleen and in the paracortical zone and medulla of lymph nodes. However, various haematopoietic or lymphoid tumor cell lines different from a lineage of monocyte/macrophage were shown to express Fgr molecule by immune complex kinase assay. Although normal resting haematopoietic or lymphoid cells

did not express Fgr protein, activated T and B cells expressed Fgr. In the presence of a mild detergent, the Fgr was co-immunoprecipitated with a 75 kDa protein (p75) and several other molecules expressed on the cell surface membrane. Furthermore, the molecule co-immunoprecipitated with Ly6C molecule from a macrophage cell line showed protein tyrosine kinase (PTK) activity. Peptide mapping showed that this kinase activity was derived from Fgr. The similarity of the relationship between this intramembrane p75 and/or Ly6C and the cytoplasmic Fgr to the relationships previously reported between T cell antigen receptor complex including CD4 and CD8 coreceptors, and Lck or Fyn in T cells and between surface IgM and Lyn or Blk in B cells suggested that the Fgr and p75 or Ly6C are indeed associated each other and responsible for recognition of extracellular substances (either cellular or non-cellular) and for signal transduction. It seems likely that these molecules are involved in activation of cells of monocyte/macrophage lineage.

L11 ANSWER 18 OF 33 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 1994:34619 BIOSIS
DOCUMENT NUMBER: PREV199497047619
TITLE: Met expression and sarcoma tumorigenicity.
AUTHOR(S): Rong, Sing; Jeffers, Michael; Resau, James H.; Tsarfaty, Ilan; Oskarsson, Marianne; Vande Woude, George F. [Reprint author]
CORPORATE SOURCE: ABL-Basic Res. Program, Natl. Cancer Inst., Frederick Cancer Res. and Dev. Cent., Frederick, MD 21702, USA
SOURCE: Cancer Research, (1993) Vol. 53, No. 22, pp. 5355-5360.
CODEN: CNREA8. ISSN: 0008-5472.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 27 Jan 1994
Last Updated on STN: 25 Mar 1994

AB The met protooncogene tyrosine kinase receptor (Met) and its ligand, hepatocyte growth factor/scatter factor (HGF/SF), ordinarily constitute a paracrine signaling system in which cells of mesenchymal origin produce the ligand, which binds to the receptor that is predominantly expressed in cells of epithelial origin. However, mouse NIH/3T3 fibroblasts overexpressing Met induce tumor formation in nude mice via an autocrine mechanism (S. Rong et al, Mol. Cell. Biol., 12: 5152-5158, 1992). In this study, we report that human cell lines established from various sarcomas express high levels of activated Met receptor. HGF/SF is also detected in the human sarcoma cell lines but at a reduced level when compared to primary fibroblasts. These properties, high Met expression and reduced ligand levels, are indistinguishable from the properties of NIH/3T3 tumor explant cells overexpressing Met (S. Rong et al., Mol. Cell. Biol., 12: 5152-5158, 1992; S. Rong et al., Cell Growth and Differ., 4: 563-569, 1993). Moreover, paraffin-embedded sections of primary tumors from human osteosarcomas, chondrosarcomas, and leiomyosarcoma stain intensely for Met and/or HGF/SF and display extensive tumor cell heterogeneity with regard to both paracrine and autocrine stimulation. On the basis of these findings, we propose that Met-HGF/SF autocrine signaling may contribute to the tumorigenic process in human sarcomas.

L11 ANSWER 19 OF 33 LIFESCI COPYRIGHT 2005 CSA on STN

ACCESSION NUMBER: 95:54576 LIFESCI
TITLE: Genetic testing for multiple endocrine neoplasia
AUTHOR: Lairmore, T.C.; Wells, S.A., Jr.
CORPORATE SOURCE: Dep. Surg., Washington Univ. Sch. Med., 660 S. Euclid Ave., St Louis, MO 63110, USA
SOURCE: BR. J. SURG., (1993) vol. 80, no. 9, pp. 1092-1093.
DOCUMENT TYPE: Journal
FILE SEGMENT: W3

LANGUAGE: English

AB Virtually all patients with MEN 2A develop medullary thyroid carcinoma (MTC); approximately half will develop clinical or biochemical evidence of either pheochromocytoma or parathyroid hyperplasia. Patients with the rare MEN 2B syndrome have MTC, pheochromocytoma, mucosal neuroma and ganglioneuromatosis of the gastrointestinal tract. They also have a characteristic phenotype. Patients with familial MTC inherit only MTC and have none of the extrathyroid manifestations characteristic of MEN 2A or 2B. Until recently, the standard for early diagnosis of MTC in patients at risk for MEN 2A was the measurement of plasma calcitonin levels by radioimmunoassay following stimulation with the calcitonin secretagogues calcium and pentagastrin. The demonstration that the gene(s) for the distinct clinical syndromes MEN 2A, MEN 2B and familial MTC each map to the centromere region of chromosome 10 was followed by the advent of DNA-based testing to identify individuals who have inherited the disease mutation before the time that they manifested either clinical or biochemical evidence of MTC. Very recently, work in our own and other laboratories has identified germline mutations in the RET proto-oncogene, a tyrosine kinase receptor gene on chromosome 10. These mutations are associated with the MEN 2A and familial MTC syndromes. Mulligan and co-workers identified missense mutations in 20 of 23 apparently distinct families with MEN 2A. Similarly, Donis-Keller and colleagues identified 12 different mutations in the germline DNA and tumour DNA from patients with MEN 2A and familial MTC. Each of the mutations described in these studies involves a codon for a highly conserved cysteine residue within the extracellular domain of the RET **proto-oncogene tyrosine kinase** receptor.

L11 ANSWER 20 OF 33 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 1993:400972 BIOSIS

DOCUMENT NUMBER: PREV199345059797

TITLE: Mutation of tyrosine-713 in the p93-c-fes **proto-oncogene tyrosine kinase** attenuates some of its catalytic and myeloid differentiating activities.

AUTHOR(S): Fang, F.; Ahmad, S.; Lei, J.; Smithgall, T. E.; Glazer, R. I.

CORPORATE SOURCE: Dep. Pharmacol., Georgetown Univ., Washington, DC 20007, USA

SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (1993) Vol. 34, No. 0, pp. 519.
Meeting Info.: 84th Annual Meeting of the American Association for Cancer Research. Orlando, Florida, USA. May 19-22, 1993.
ISSN: 0197-016X.

DOCUMENT TYPE: Conference; (Meeting)

LANGUAGE: English

ENTRY DATE: Entered STN: 30 Aug 1993

Last Updated on STN: 3 Jan 1995

L11 ANSWER 21 OF 33 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 1992:523465 BIOSIS

DOCUMENT NUMBER: PREV199294131540; BA94:131540

TITLE: AN EXTRA CYSTEINE PROXIMAL TO THE TRANSMEMBRANE DOMAIN INDUCES DIFFERENTIAL CROSS-LINKING OF P185N-E-U AND P185N-E-U.

AUTHOR(S): CAO H [Reprint author]; BANGALORE L; DOMPE C; BORMANN B-J; STERN D F

CORPORATE SOURCE: DEP PATHOLOGY, YALE UNIVERSITY SCHOOL MEDICINE, NEW HAVEN, CONN 06510, USA

SOURCE: Journal of Biological Chemistry, (1992) Vol. 267, No. 28,

pp. 20489-20492.
CODEN: JBCHA3. ISSN: 0021-9258.

DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 19 Nov 1992
Last Updated on STN: 20 Nov 1992

AB The neu proto-oncogene encodes a receptor tyrosine kinase (p 185) that is closely related to the epidermal growth factor receptor. It has been proposed that receptor tyrosine kinases are activated through oligomerization. Because this clustering model predicts that oligomerization of receptors is sufficient to activate them, we determined if p185 can be activated by introducing an extra cysteine proximal to the transmembrane domain. This should induce inter-receptor disulfide bonding and, according to the clustering model, activate the receptor. This amino acid substitution enhanced recovery of both normal and transforming neu proteins as dimers, with normal p185 recovered predominantly as monomers and transforming p185. as dimers. However, the cysteine substitution did not affect the transforming activity of the two proteins.

L11 ANSWER 22 OF 33 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 1992:363476 BIOSIS
DOCUMENT NUMBER: PREV199243041626; BR43:41626
TITLE: MODULATION OF THE C-KIT RECEPTOR IN BREAST CARCINOMA.
AUTHOR(S): NATALI P G [Reprint author]; NICOTRA M R; SURES I; BIGOTTI A; ULLRICH A
CORPORATE SOURCE: REGINA ELENA CANCER INST, ROME, ITALY
SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (1992) Vol. 33, pp. 22.
Meeting Info.: 83RD ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH, SAN DIEGO, CALIFORNIA, USA, MAY 20-23, 1992. PROC AM ASSOC CANCER RES ANNU MEET. ISSN: 0197-016X.
DOCUMENT TYPE: Conference; (Meeting)
FILE SEGMENT: BR
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 30 Jul 1992
Last Updated on STN: 30 Jul 1992

L11 ANSWER 23 OF 33 MEDLINE on STN DUPLICATE 9

ACCESSION NUMBER: 91264781 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1646596
TITLE: Purification and characterization of a higher-molecular-mass form of protein phosphotyrosine phosphatase (PTP 1B) from placental membranes.
AUTHOR: Pallen C J; Lai D S; Chia H P; Boulet I; Tong P H
CORPORATE SOURCE: Institute of Molecular and Cell Biology, National University of Singapore.
SOURCE: Biochemical journal, (1991 Jun 1) 276 (Pt 2) 315-23. Journal code: 2984726R. ISSN: 0264-6021.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199107
ENTRY DATE: Entered STN: 19910802
Last Updated on STN: 19970203
Entered Medline: 19910717

AB Purification of a major placental membrane protein phosphotyrosine phosphatase (PTP-I) through the use of a nonhydrolysable phosphotyrosine analogue affinity ligand has enabled identification of the enzyme as a single polypeptide of at least 46 kDa. This phosphatase specifically

dephosphorylates phosphotyrosine-containing substrates, including the src peptide, the epidermal-growth-factor receptor tyrosine kinase and the non-receptor tyrosine kinase p56lck. The p56lck can be dephosphorylated by PTP-I at two tyrosine residues (Tyr-394 and Tyr-505), which are differentially phosphorylated in vitro and in vivo and have been suggested to modulate kinase activity. The activity of PTP-I towards these substrates indicates a possible function of regulation of cellular tyrosine phosphorylation pathways at the level of growth-factor receptor and/or oncogene/**proto-oncogene tyrosine**

kinases. Kinetic analyses show that PTP-I exhibits a Km value of about 2 microm with either src peptide or reduced, carboxyamidomethylated and maleylated (RCM)-lysozyme as substrate, and is inhibited in a mixed competitive manner by the polyanions heparin and poly(Glu4,Tyr1). Sequencing of PTP-I peptides reveals almost complete identity with sequences within the N-terminal half of the 37 kDa non-receptor tyrosine phosphatase 1B. However, the size and amino acid composition of PTP-I are similar to that of a higher-molecular-mass form of PTP 1B predicted from cDNA cloning. These results suggest that the 37 kDa PTP 1B is a proteolysed form of PTP-I, and provide evidence that a larger form of PTP 1B exists in vivo, at least in association with placental membranes.

L11 ANSWER 24 OF 33 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 1991:539660 BIOSIS
DOCUMENT NUMBER: PREV199141129395; BR41:129395
TITLE: EXPRESSION PROFILE OF C-KIT AND ITS LIGAND KL IN
HEMATOPOIETIC PROGENITOR COLONIES AND BONE MARROW STROMAL
CELLS.
AUTHOR(S): NARAYANAN R [Reprint author]; SCHAAPELDE R Q J; TARE N S;
HIGGINS K A; BENJAMIN W R
CORPORATE SOURCE: DEP MOLECULAR GENETICS, ROCHE RES CENT, HOFFMANN-LA ROCHE
INC, NUTLEY, NJ 07110, USA
SOURCE: Journal of Leukocyte Biology, (1991) No. SUPPL. 2, pp. 90.
Meeting Info.: TWENTY-EIGHTH NATIONAL MEETING OF THE
SOCIETY FOR LEUKOCYTE BIOLOGY AND THE TWENTY-FIRST
LEUKOCYTE CULTURE CONFERENCE, ASPEN, COLORADO, USA,
SEPTEMBER 28-OCTOBER 1, 1991. J LEUKOCYTE BIOL.
CODEN: JLBIE7. ISSN: 0741-5400.
DOCUMENT TYPE: Conference; (Meeting)
FILE SEGMENT: BR
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 25 Nov 1991
Last Updated on STN: 26 Nov 1991

L11 ANSWER 25 OF 33 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 1991:196666 BIOSIS
DOCUMENT NUMBER: PREV199140093946; BR40:93946
TITLE: INSULIN-STIMULATED ACTIVATION OF THE RAF-1 PROTEIN KINASE.
AUTHOR(S): LEE R-M [Reprint author]; BLACKSHEAR P J
CORPORATE SOURCE: HOWARD HUGHES MED INST LAB, DURHAM, NC 27710, USA
SOURCE: Journal of Cellular Biochemistry Supplement, (1991) No. 15
PART B, pp. 43.
Meeting Info.: SYMPOSIUM ON DIABETES AND INSULIN ACTION
HELD AT THE 20TH ANNUAL MEETING OF THE KEYSTONE SYMPOSIA ON
MOLECULAR AND CELLULAR BIOLOGY, PARK CITY, UTAH, USA,
JANUARY 18-24, 1991. J CELL BIOCHEM SUPPL.
ISSN: 0733-1959.
DOCUMENT TYPE: Conference; (Meeting)
FILE SEGMENT: BR
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 22 Apr 1991
Last Updated on STN: 14 Jun 1991

L11 ANSWER 26 OF 33 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 1990:310993 BIOSIS
DOCUMENT NUMBER: PREV199090029960; BA90:29960
TITLE: PROTEIN KINASE-C ACTIVATION INHIBITS TYROSINE
PHOSPHORYLATION OF THE C-MET PROTEIN.
AUTHOR(S): GANDINO L [Reprint author]; FLAVIA DI RENZO M; GIORDANO S;
BUSSOLINO F; COMOGLIO P M
CORPORATE SOURCE: DEP BIOMED SCI ONCOL, UNIV TORINO, CSO MD'AZEGLIO 52, 10126
TORINO, ITALY
SOURCE: Oncogene, (1990) Vol. 5, No. 5, pp. 721-726.
CODEN: ONCNES. ISSN: 0950-9232.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 10 Jul 1990
Last Updated on STN: 10 Jul 1990

AB The mature product of the c-met proto-oncogene is a putative tyrosine kinase receptor of 190 kd with an $\alpha\beta$ heterodimeric structure. The c-met protein is phosphorylated in vivo on the β subunit in the gastric carcinoma cell line GTL-16 (Giordano et al., 1988). Western blots with phosphotyrosine antibodies show that tyrosine phosphorylation of the β subunit is reduced by treatment of GTL-16 cells with protein kinase C activators (tumor promoting phorbol esters such as phorbol 12-myristate 13-acetate, TPA, and β -phorbol 12,13-dibutyrate, PdBu, or membrane permeable synthetic diacylglycerol 1-oleyl-2-acetyl-sn-glycerol, OAG). The inactive analog α -phorbol 12,13-didecanoate has no effect. The inhibition induced by TPA is dose dependent and maximal after 1 h. Depletion of protein kinase-C by prolonged treatment with TPA (18-48 h) increases the phosphorylation on tyrosine of the β subunit. Phospho-amino acid analysis of the c-met protein immunoprecipitated from [32P]orthophosphate-labelled GTL-16 cells shows that protein kinase-C activation leads to an increase in serine phosphorylation and to concomitant decrease in tyrosine phosphorylation. These results suggest that, similar to the EGF and insulin receptor, the putative receptor encoded by the c-met proto-oncogene may be negatively modulated by protein kinase-C phosphorylation.

L11 ANSWER 27 OF 33 MEDLINE on STN DUPLICATE 10

ACCESSION NUMBER: 89261807 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2786142
TITLE: Functional heterogeneity of **proto-oncogene tyrosine kinases**: the C terminus of the human epidermal growth factor receptor facilitates cell proliferation.
AUTHOR: Velu T J; Vass W C; Lowy D R; Beguinot L
CORPORATE SOURCE: Laboratory of Cellular Oncology, National Cancer Institute, Bethesda, Maryland 20892.
SOURCE: Molecular and cellular biology, (1989 Apr) 9 (4) 1772-8.
Journal code: 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198907
ENTRY DATE: Entered STN: 19900309
Last Updated on STN: 20000303
Entered Medline: 19890705

AB Previous reports have indicated that the C termini of the membrane-associated tyrosine kinases encoded by c-src and c-fms proto-oncogenes have a negative effect on their biological activity and that this effect is mediated by their C-terminal tyrosine residue. To

determine whether this was true for the human epidermal growth factor (EGF) receptor, which is also a membrane-associated tyrosine kinase proto-oncogene, we have constructed two premature termination mutants, dc19 and dc63, that delete the C-terminal 19 and 63 amino acids, respectively, from the human full-length receptor (hEGFR). The smaller deletion removes the C-terminal tyrosine residue, while the larger deletion removes the two most C-terminal tyrosines; similar deletions are found in v-erbB. As previously shown for the gene encoding the full-length EGF receptor, the two C-terminal mutants induced EGF-dependent focal transformation and anchorage-independent growth of NIH 3T3 cells. However, both dc19 and dc63 were quantitatively less efficient than the gene encoding the full-length receptor, with dc63 being less active than dc19. Although the C-terminal mutants displayed lower biological activity than the gene encoding the full-length receptor, the mutant receptors were found to be similar in several respects to the full-length receptor. These parameters included receptor localization, stability in the absence of EGF, receptor half-life in the presence of EGF, EGF binding, extent of EGF-dependent autophosphorylation in vitro, and EGF-dependent phosphorylation of an exogenous substrate in vitro. Therefore, the C-terminal 63 amino acids of the human receptor have no detectable influence on EGF-dependent early events. We conclude that in contrast

L11 ANSWER 28 OF 33 MEDLINE on STN DUPLICATE 11
 ACCESSION NUMBER: 89385605 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 2674853
 TITLE: Cloning of the murine c-fgr proto-oncogene cDNA and induction of c-fgr expression by proliferation and activation factors in normal bone marrow-derived monocytic cells.
 AUTHOR: Yi T L; Willman C L
 CORPORATE SOURCE: Department of Cell Biology, University of New Mexico School of Medicine, Albuquerque 87131.
 CONTRACT NUMBER: KII DK-01284 (NIDDK)
 SOURCE: Oncogene, (1989 Sep) 4 (9) 1081-7.
 Journal code: 8711562. ISSN: 0950-9232.
 PUB. COUNTRY: ENGLAND: United Kingdom
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 198910
 ENTRY DATE: Entered STN: 19900309
 Last Updated on STN: 19970203
 Entered Medline: 19891017

AB Normal murine bone marrow-derived monocytic cells were found to contain transcripts for c-fgr and hck, two members of the src family of **proto-oncogene tyrosine kinases**. While hck transcripts were increased only in response to bacterial lipopolysaccharide (LPS), expression of c-fgr was transiently induced both by the monocyte/macrophage proliferative stimulus CSF-1 as well as by signals which activate monocytic cells to functional states (granulocyte-macrophage colony stimulating factor (GM-CSF), LPS, and gamma interferon). These data suggest that these highly related tyrosine kinases may differentially mediate the effects of distinct monocyte/macrophage stimuli; and, that the c-fgr proto-oncogene in particular, which in normal cells is selectively expressed in monocytes, may play a pivotal functional role in these cells. A 2.2 kb cDNA clone, containing a 1551 base pair open reading frame encoding a protein with all of the hallmarks of a protein-tyrosine kinase, was isolated from a cDNA library made from RNA of CSF-1-stimulated bone marrow-derived monocytic cells. This clone had the highest homology to v-fgr and likely encodes the murine c-fgr transcript expressed by normal monocytes. However, when compared to sequences previously reported for human c-fgr derived from EBV-transformed B cells and heterogeneous peripheral blood cells, the

c-fgr cDNA derived from normal murine monocytic cells differed significantly in sequence from amino acids 12-62 in the amino terminal domain of the protein which may mediate the substrate specificity and subcellular location of the src family of protein-tyrosine kinases.

L11 ANSWER 29 OF 33 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 1989:449826 BIOSIS
DOCUMENT NUMBER: PREV198988098098; BA88:98098
TITLE: C-KIT MESSENGER RNA EXPRESSION IN HUMAN AND MURINE HEMATOPOIETIC CELL LINES.
AUTHOR(S): ANDRE C [Reprint author]; D'AURIOL L; LACOMBE C; GISSELBRECHT S; GALIBERT F
CORPORATE SOURCE: LAB HEMATOL EXP, HOP SAINT-LOUIS, 2 PLACE DU DR FOURNIER, 75475 PARIS CEDEX 10, FR
SOURCE: Oncogene, (1989) Vol. 4, No. 8, pp. 1047-1050.
CODEN: ONCNES. ISSN: 0950-9232.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 4 Oct 1989
Last Updated on STN: 6 Oct 1989

AB The c-kit proto-oncogene belongs to the tyrosine kinase receptor family. Although its ligand is still unknown, there is increasing evidence to suggest its involvement in hematopoiesis. In order to detect lineage or differentiation related specificity, we have studied c-kit mRNA expression in both human and murine hematopoietic organs and cell lines. We show that c-kit mRNA expression is found at early stages of erythroid and myeloid differentiation. There is however, no evidence of c-kit expression in the lymphoid lineage. Our results suggest a possible role for c-kit as a receptor in the early stages of the erythroid/myeloid differentiation.

L11 ANSWER 30 OF 33 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 1988:376533 BIOSIS
DOCUMENT NUMBER: PREV198886060443; BA86:60443
TITLE: ACQUISITION OF TRANSFORMING PROPERTIES BY FYN A NORMAL SRC-RELATED HUMAN GENE.
AUTHOR(S): KAWAKAMI T [Reprint author]; KAWAKAMI Y; AARONSON S A; ROBBINS K C
CORPORATE SOURCE: LAB CELLULAR AND MOL BIOL, NATL CANCER INST, BUILDING 37, ROOM 1E24, BETHESDA, MD 20892, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (1988) Vol. 85, No. 11, pp. 3870-3874.
CODEN: PNASA6. ISSN: 0027-8424.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 18 Aug 1988
Last Updated on STN: 18 Aug 1988

AB The SRC gene is the prototype for a family of closely related genes whose products have protein-tyrosine kinase activity. We recently described another member of this family, designated FYN, whose cDNA was isolated from normal human fibroblasts. To examine the possible role of FYN as an oncogene, we investigated the effects of FYN overexpression on NIH 3T3 cells. Our findings demonstrate that normal FYN overexpression induces morphologic transformation and anchorage-independent growth. In addition, at relatively low frequency, FYN acquired properties of a dominant-acting oncogene capable of inducing the fully tumorigenic phenotype. Genetic changes associated with the conversion of normal FYN cDNA into a transforming gene with high focus-forming activity were localized to the

carboxyl-terminal region of its translational product.

L11 ANSWER 31 OF 33 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 1989:95930 BIOSIS
DOCUMENT NUMBER: PREV198987050066; BA87:50066
TITLE: PEPTIDE ANTIBODIES TO THE HUMAN C-FYN GENE PRODUCT
DEMONSTRATE PP59C-F-Y-N IS CAPABLE OF COMPLEX FORMATION
WITH THE MIDDLE-T ANTIGEN OF POLYOMAVIRUS.
AUTHOR(S): CHENG S H [Reprint author]; HARVEY R; ESPINO P C; SEMBA K;
YAMAMOTO T; TOYOSHIMA K; SMITH A E
CORPORATE SOURCE: LAB CELLULAR REGULATION, INTEGRATED GENETICS, INC, ONE
MOUNTAIN RD, FRAMINGHAM, MASS 07101, USA
SOURCE: EMBO (European Molecular Biology Organization) Journal,
(1988) Vol. 7, No. 12, pp. 3845-3856.
CODEN: EMJODG. ISSN: 0261-4189.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 6 Feb 1989
Last Updated on STN: 6 Feb 1989

AB The c-fyn proto-oncogene is a member of a family of closely related genes of which c-src is the prototype. Using peptide antibodies which had been raised against sequences predicted to be specific for the human c-fyn gene product, the c-fyn protein was identified. It is a tyrosine kinase with apparent mol. wt of 59 kd that is also phosphorylated and myristylated. Like pp60c-src and pp62c-yes, pp59c-fyn is able to form a stable complex with middle-T antigen, the transforming protein of polyomavirus. The transformation-defective middle-T mutant NG59, which is unable to associate stably with pp60c-src does not associate with pp59c-fyn. In contrast to pp60c-src, complex formation with middle-T antigen does not lead to a significant increase in the tyrosine kinase activity of pp59c-fyn. These findings lead us to suggest that middle-T mediated transformation may be a consequence of the deregulation of several members of the src-family of protein tyrosine kinases.

L11 ANSWER 32 OF 33 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 1989:148840 BIOSIS
DOCUMENT NUMBER: PREV198936070881; BR36:70881
TITLE: TRANSFORMING POTENTIAL OF THE HUMAN CSF-1 RECEPTOR.
AUTHOR(S): SHERR C J [Reprint author]; DOWNING J R; RETTENMIER C W;
ROUSSEL M F
CORPORATE SOURCE: ST JUDE CHILDREN'S RES HOSP, MEMPHIS, TN, USA
SOURCE: Journal of Cell Biology, (1988) Vol. 107, No. 6 PART 3, pp. 9A.
Meeting Info.: JOINT MEETING OF THE AMERICAN SOCIETY FOR
CELL BIOLOGY AND THE AMERICAN SOCIETY FOR BIOCHEMISTRY AND
MOLECULAR BIOLOGY, SAN FRANCISCO, CALIFORNIA, USA, JANUARY
29-FEBRUARY 2, 1989. J CELL BIOL.
CODEN: JCLBA3. ISSN: 0021-9525.
DOCUMENT TYPE: Conference; (Meeting)
FILE SEGMENT: BR
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 13 Mar 1989
Last Updated on STN: 13 Mar 1989

L11 ANSWER 33 OF 33 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 1987:350354 BIOSIS
DOCUMENT NUMBER: PREV198733050975; BR33:50975
TITLE: CHARACTERIZATION OF PHOSPHOPROTEINS IN SPONGES.
AUTHOR(S): HIRSCH A [Reprint author]; BARNEKOW A

CORPORATE SOURCE: INST MED VIROL, UNIV GIESSEN, FRANKFURTER STR 107, D-6300
 GIESSEN, FRG
 SOURCE: European Journal of Cell Biology Supplement, (1987) No. 17,
 pp. 26.
 Meeting Info.: SYMPOSIUM ON BIOGENESIS OF ORGANELLES, ION
 TRANSPORT, CELL POLARITY AND CELL PROLIFERATION HELD AT THE
 ANNUAL MEETING OF THE DEUTSCHE GESELLSCHAFT FUER
 ZELLBIOLOGIE (GERMAN SOCIETY OF CELL BIOLOGY), HEIDELBERG,
 WEST GERMANY, MARCH 16-20, 1987. EUR J CELL BIOL SUPPL.
 ISSN: 0724-5130.
 DOCUMENT TYPE: Conference; (Meeting)
 FILE SEGMENT: BR
 LANGUAGE: ENGLISH
 ENTRY DATE: Entered STN: 15 Aug 1987
 Last Updated on STN: 15 Aug 1987

=> d his

(FILE 'HOME' ENTERED AT 12:43:08 ON 02 AUG 2005)

FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
 LIFESCI' ENTERED AT 12:43:44 ON 02 AUG 2005

L1	219065	S TYROSINE (A)KINASE?
L2	117272	S PROTO(W)ONCOGENE
L3	19359	S L1 AND L2
L4	11988	S HUMAN AND L3
L5	7194083	S CLON? OR EXPRESS? OR RECOMBINANT
L6	8010	S L4 AND L5
L7	1361302	S UTERUS OR LEUKEMIA OR ADENOCARCINOMA
L8	1451	S L6 AND L7
L9	5	S L8 AND HIPPOCAMPUS
L10	67	S L2(W)L1
L11	33	DUP REM L10 (34 DUPLICATES REMOVED)

=> e gan w/au

E1	6	GAN VANTHAYA N/AU
E2	1	GAN VICTOR/AU
E3	98 -->	GAN W/AU
E4	1	GAN W A/AU
E5	91	GAN W B/AU
E6	4	GAN W C/AU
E7	28	GAN W E/AU
E8	8	GAN W H/AU
E9	31	GAN W J/AU
E10	4	GAN W L/AU
E11	11	GAN W M/AU
E12	7	GAN W N/AU

=> s e3

L12 98 "GAN W"/AU

=> e difrancesco v/au

E1	1	DIFRANCESCO U/AU
E2	1	DIFRANCESCO U M/AU
E3	80 -->	DIFRANCESCO V/AU
E4	17	DIFRANCESCO VALENTINA/AU
E5	1	DIFRANCESCO L/AU
E6	1	DIFRANCESCO D/AU
E7	2	DIFRANCESCO L/AU
E8	1	DIFRANCESCO R/AU
E9	1	DIFRANCESCO ROBIN/AU
E10	6	DIFRANCIA C/AU

E11 4 DIFRANCIA CELENE/AU
E12 13 DIFRANCIA G/AU

=> s e3-e4

L13 97 ("DIFRANCESCO V"/AU OR "DIFRANCESCO VALENTINA"/AU)

=> e beasley e m/au

E1 1 BEASLEY E H/AU
E2 6 BEASLEY E L/AU
E3 330 --> BEASLEY E M/AU
E4 7 BEASLEY E O/AU
E5 1 BEASLEY E S G/AU
E6 2 BEASLEY E T/AU
E7 4 BEASLEY E W/AU
E8 2 BEASLEY E W 3RD/AU
E9 2 BEASLEY E W III/AU
E10 1 BEASLEY E W JR/AU
E11 1 BEASLEY EDWARD E/AU
E12 1 BEASLEY EDWARD EVANS/AU

=> s e3

L14 330 "BEASLEY E M"/AU

=> d his

(FILE 'HOME' ENTERED AT 12:43:08 ON 02 AUG 2005)

FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS, LIFESCI' ENTERED AT 12:43:44 ON 02 AUG 2005

L1 219065 S TYROSINE (A) KINASE?
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L3 19359 S L1 AND L2
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L7 1361302 S UTERUS OR LEUKEMIA OR ADENOCARCINOMA
L8 1451 S L6 AND L7
L9 5 S L8 AND HIPPOCAMPUS
L10 67 S L2(W) L1
L11 33 DUP REM L10 (34 DUPLICATES REMOVED)
E GAN W/AU
L12 98 S E3
E DIFRANCESCO V/AU
L13 97 S E3-E4
E BEASLEY E M/AU
L14 330 S E3

=> e ye j/au

E1 2 YE IN HAE/AU
E2 1 YE INN SUK/AU
E3 1947 --> YE J/AU
E4 1 YE JRX/AU
E5 17 YE J A/AU
E6 243 YE J B/AU
E7 42 YE J C/AU
E8 44 YE J D/AU
E9 23 YE J F/AU
E10 14 YE J G/AU
E11 402 YE J H/AU
E12 142 YE J J/AU

=> s e3

L15 1947 "YE J"/AU

=> s l12 or l13 or l14 or l15
L16 2366 L12 OR L13 OR L14 OR L15.

=> s l4 and l16
L17 1 L4 AND L16

=> d all

L17 ANSWER 1 OF 1 BIOTECHDS COPYRIGHT 2005 THE THOMSON CORP. on STN

AN 2002-07016 BIOTECHDS

TI Nucleic acids encoding a **proto-oncogene tyrosine kinase**, useful for the prevention, diagnosis and treatment of e.g. leukemia and lung tumors;
tyrosine-kinase gene transfer by vector expression in host cell for cancer gene therapy

AU **GAN W; YE J; DI FRANCESCO V; BEASLEY E M**

PA PE CORP NY

PI US 6340584 22 Jan 2002

AI US 2001-817180 27 Mar 2001

PRAI US 2001-817180 27 Mar 2001

DT Patent

LA English

OS WPI: 2002-138497 [18]

AB DERWENT ABSTRACT:

NOVELTY - Isolated nucleic acid sequences (I) encoding a **proto-oncogene tyrosine kinase** (poTK), is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following: (1) an isolated nucleic acid molecule (I) comprising a nucleotide sequence selected from: (a) a nucleotide sequence that encodes a defined 752 amino acid sequence (A1) given in the specification; (b) a nucleic acid molecule comprising a defined 2674 nucleotide sequence (N1) given in the specification; (c) a nucleic acid molecule consisting of a defined 15297 nucleotide sequence (N2) given in the specification; and (d) a nucleotide sequence that is completely complementary to a nucleotide sequence of (a)-(c); (2) a nucleic acid vector (II) comprising (I); (3) a host cell (IV) containing (III); and (4) a process (V) for producing a polypeptide comprising culturing the host cell (IV) under conditions sufficient for the production of the polypeptide, and recovering the peptide from the host cell culture.

BIOTECHNOLOGY - Preferred Nucleic Acid Molecules: (I) Comprises (N1) or (N2). Preferred Vectors: (II) Is a plasmid, virus or bacteriophage. The isolated nucleic acid molecule is inserted into the vector in proper orientation and correct reading frame so that the protein of (A1) may be expressed by a cell transformed with the vector. The isolated nucleic acid molecule is operatively linked to a promoter sequence. Preparation: (I) Has been isolated from **human** placenta, lung tumors, kidney tumors, pregnant uterus, leukemia, stomach adenocarcinoma, and hippocampus, via standard methodologies. The poTK it encodes may be produced by culturing (IV).

ACTIVITY - Cytostatic; Anti-leukemic. No biological data given.

MECHANISM OF ACTION - Gene therapy; Protein therapy; Vaccine; Enzymatic-inhibition; Anti-kinase.

USE - (I) and the poTK may be used in the prevention, diagnosis and treatment of diseases associated with inappropriate poTK expression, such as lung and kidney tumors, leukemia and stomach adenocarcinoma. For example, (I) (or (II)) and poTK may be used to treat disorders associated with decreased expression by rectifying mutations or deletions in a patient's genome that affect the activity of poTK by expressing inactive proteins or to supplement the patients own production of poTK. Additionally, (I) and (II) may be used to produce the poTK, by inserting the nucleic acid into a host cell (III) and culturing the cell to express the protein (V). (I) and its complementary sequences may also be used as

DNA probes in diagnostic assays to detect and quantitate the presence of similar nucleic acids in samples, and therefore which patients may be in need of restorative therapy. The encoded poTK may be used as an antigen in the production of antibodies against poTK and in assays to identify modulators of poTK expression and activity. The anti-poTK antibodies and antagonists may be used to down regulate expression and activity and as diagnostic agents for detecting the presence of poTK in samples.

ADMINISTRATION - No details given. (49 pages)

CC THERAPEUTICS, Gene Therapy; GENETIC TECHNIQUES and APPLICATIONS, Gene Expression Techniques and Analysis; DISEASE, Cancer; DISEASE, Blood and Hematopoietic Cells; THERAPEUTICS, Protein Therapeutics; PHARMACEUTICALS, Vaccines; DIAGNOSTICS, Antibody-Based Diagnostics; DIAGNOSTICS, Molecular Diagnostics

CT **TYROSINE-KINASE PROTO-ONCOGENE**
PREP., PURIFICATION, VIRUS VECTOR PLASMID, PHAGE-MEDIATED GENE TRANSFER, EXPRESSION IN HOST CELL, ANTISENSE, DNA PROBE, ANTIBODY, ANTAGONIST, APPL. LUNG, KIDNEY, STOMACH CANCER, LEUKEMIA THERAPY, GENE THERAPY, DIAGNOSIS, RECOMBINANT VACCINE, NUCLEIC ACID VACCINE ENZYME EC-2.7.1.112
TUMOR DNA SEQUENCE PROTEIN SEQUENCE (21, 26)

=> d his

(FILE 'HOME' ENTERED AT 12:43:08 ON 02 AUG 2005)

FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS, LIFESCI' ENTERED AT 12:43:44 ON 02 AUG 2005

L1 219065 S TYROSINE (A)KINASE?
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L10 67 S L2(W)L1
L11 33 DUP REM L10 (34 DUPLICATES REMOVED)
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L12 98 S E3
E DIFRANCESCO V/AU
L13 97 S E3-E4
E BEASLEY E M/AU
L14 330 S E3
E YE J/AU
L15 1947 S E3
L16 2366 S L12 OR L13 OR L14 OR L15
L17 1 S L4 AND L16

=> s l1 and l3

L18 19359 L1 AND L3

=> s l16 and l18

L19 1 L16 AND L18

=> s l16 and l3

L20 1 L16 AND L3

=> d all

L20 ANSWER 1 OF 1 BIOTECHDS COPYRIGHT 2005 THE THOMSON CORP. on STN

AN 2002-07016 BIOTECHDS

TI Nucleic acids encoding a **proto-oncogene**

tyrosine kinase, useful for the prevention, diagnosis and treatment of e.g. leukemia and lung tumors;

tyrosine-kinase gene transfer by vector expression in host cell for cancer gene therapy

AU **GAN W; YE J; DI FRANCESCO V; BEASLEY E M**

PA PE CORP NY

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PRAI US 2001-817180 27 Mar 2001

DT Patent

LA English

OS WPI: 2002-138497 [18]

AB DERWENT ABSTRACT:

NOVELTY - Isolated nucleic acid sequences (I) encoding a **proto-oncogene tyrosine kinase** (poTK), is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following: (1) an isolated nucleic acid molecule (I) comprising a nucleotide sequence selected from: (a) a nucleotide sequence that encodes a defined 752 amino acid sequence (A1) given in the specification; (b) a nucleic acid molecule comprising a defined 2674 nucleotide sequence (N1) given in the specification; (c) a nucleic acid molecule consisting of a defined 15297 nucleotide sequence (N2) given in the specification; and (d) a nucleotide sequence that is completely complementary to a nucleotide sequence of (a)-(c); (2) a nucleic acid vector (II) comprising (I); (3) a host cell (IV) containing (III); and (4) a process (V) for producing a polypeptide comprising culturing the host cell (IV) under conditions sufficient for the production of the polypeptide, and recovering the peptide from the host cell culture.

BIOTECHNOLOGY - Preferred Nucleic Acid Molecules: (I) Comprises (N1) or (N2). Preferred Vectors: (II) Is a plasmid, virus or bacteriophage. The isolated nucleic acid molecule is inserted into the vector in proper orientation and correct reading frame so that the protein of (A1) may be expressed by a cell transformed with the vector. The isolated nucleic acid molecule is operatively linked to a promoter sequence. Preparation: (I) Has been isolated from human placenta, lung tumors, kidney tumors, pregnant uterus, leukemia, stomach adenocarcinoma, and hippocampus, via standard methodologies. The poTK it encodes may be produced by culturing (IV).

ACTIVITY - Cytostatic; Anti-leukemic. No biological data given.

MECHANISM OF ACTION - Gene therapy; Protein therapy; Vaccine; Enzymatic-inhibition; Anti-kinase.

USE - (I) and the poTK may be used in the prevention, diagnosis and treatment of diseases associated with inappropriate poTK expression, such as lung and kidney tumors, leukemia and stomach adenocarcinoma. For example, (I) (or (II)) and poTK may be used to treat disorders associated with decreased expression by rectifying mutations or deletions in a patient's genome that affect the activity of poTK by expressing inactive proteins or to supplement the patients own production of poTK. Additionally, (I) and (II) may be used to produce the poTK, by inserting the nucleic acid into a host cell (III) and culturing the cell to express the protein (V). (I) and its complementary sequences may also be used as DNA probes in diagnostic assays to detect and quantitate the presence of similar nucleic acids in samples, and therefore which patients may be in need of restorative therapy. The encoded poTK may be used as an antigen in the production of antibodies against poTK and in assays to identify modulators of poTK expression and activity. The anti-poTK antibodies and antagonists may be used to down regulate expression and activity and as diagnostic agents for detecting the presence of poTK in samples.

ADMINISTRATION - No details given. (49 pages)

CC THERAPEUTICS, Gene Therapy; GENETIC TECHNIQUES and APPLICATIONS, Gene Expression Techniques and Analysis; DISEASE, Cancer; DISEASE, Blood and Hematopoietic Cells; THERAPEUTICS, Protein Therapeutics; PHARMACEUTICALS, Vaccines; DIAGNOSTICS, Antibody-Based Diagnostics; DIAGNOSTICS, Molecular

Diagnostics

CT **TYROSINE-KINASE PROTO-ONCOGENE**
PREP., PURIFICATION, VIRUS VECTOR PLASMID, PHAGE-MEDIATED GENE TRANSFER,
EXPRESSION IN HOST CELL, ANTISENSE, DNA PROBE, ANTIBODY, ANTAGONIST,
APPL. LUNG, KIDNEY, STOMACH CANCER, LEUKEMIA THERAPY, GENE THERAPY,
DIAGNOSIS, RECOMBINANT VACCINE, NUCLEIC ACID VACCINE ENZYME EC-2.7.1.112
TUMOR DNA SEQUENCE PROTEIN SEQUENCE (21, 26)

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L13 97 S E3-E4
E BEASLEY E M/AU
L14 330 S E3
E YE J/AU
L15 1947 S E3
L16 2366 S L12 OR L13 OR L14 OR L15
L17 1 S L4 AND L16
L18 19359 S L1 AND L3
L19 1 S L16 AND L18
L20 1 S L16 AND L3

=> s l1 and l16

L21 12 L1 AND L16

=> dup rem l21

PROCESSING COMPLETED FOR L21

L22 9 DUP REM L21 (3 DUPLICATES REMOVED)

=> d 1-9 ibib ab

L22 ANSWER 1 OF 9 BIOTECHDS COPYRIGHT 2005 THE THOMSON CORP. on STN

ACCESSION NUMBER: 2003-00789 BIOTECHDS

TITLE: New isolated human kinase proteins and genes, useful in
developing drugs, as well as for diagnosing, preventing or
treating disorders associated with defective cell signal
transduction, e.g. cancer or hematopoietic disorders;
vector-mediated gene transfer and expression in host cell
for recombinant protein production, drug screening and
gene therapy

AUTHOR: **BEASLEY E M**; SHAO W; KETCHUM K; DI FRANCESCO V

PATENT ASSIGNEE: PE CORP NY

PATENT INFO: WO 2002052018 4 Jul 2002

APPLICATION INFO: WO 2001-US48546 19 Dec 2001

PRIORITY INFO: US 2000-741154 21 Dec 2000; US 2000-741154 21 Dec 2000

DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2002-583568 [62]
AB DERWENT ABSTRACT:

NOVELTY - An isolated human kinase peptide that comprises a 415 residue amino acid sequence (I), given in the specification, is an allelic variant of (I), which is encoded by a nucleic acid that hybridizes under stringent conditions to the opposite strand of a 1713 (II) or 16389 (III) base pair sequence, given in the specification, is a fragment of (I) comprising at least 10 contiguous amino acids, or shares at least 70 % homology to (I), is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following: (1) an isolated antibody that selectively binds to the novel human kinase peptide; (2) an isolated nucleic acid molecule that: (a) encodes the novel human kinase peptide; (b) is the complement of (a); or (c) shares at least 80% homology with (II) or (III); (3) a gene chip comprising the nucleic acid of (2) (4) a transgenic non-human animal comprising the nucleic acid of (2); (5) a nucleic acid vector comprising the nucleic acid of (2); (6) a host cell containing the vector of (5); (7) producing the novel human kinase peptides; (8) detecting the presence of any of the peptides in a sample, comprising contacting the sample with a detection agent that specifically allows detection of the presence of the peptide in the sample, and detecting the peptide; (9) detecting the presence of the nucleic acid in a sample, comprising: (a) contacting a sample with an oligonucleotide that hybridizes to the nucleic acid under stringer conditions; and (b) determining if the oligonucleotide binds to the nucleic acid molecule in the sample; (10) identifying modulators of: (a) the novel human kinase peptide by contacting the peptide with an agent and determining if the agent has modulated the function or activity of the peptide; or (b) the expression of the novel peptide by contacting a cell expressing the peptide with an agent and determining if the agent has modulated the expression of the peptide; and (11) identifying an agent that binds to the human kinase peptides by contacting the peptide with an agent, and assaying the contacted mixture to determine if a complex is formed with the agent bound to the peptide.

BIOTECHNOLOGY - Preferred Peptide: The peptide shares at least 90 % homology with the amino acid sequence (I). The peptide is preferably encoded by a nucleic acid molecule that shares at least 90 % homology with the nucleotide sequence (II) or (III). Preferred Method: In the method (10a) for identifying a modulator of a human kinase peptide, the agent is administered to a host cell comprising an expression vector that expresses the peptide. Preparation: The human kinase peptide is produced by: (a) introducing a nucleotide sequence encoding any of the novel human kinases, in to a host cell; and (b) culturing the host cell under expression conditions.

ACTIVITY - Hemostatic; Cytostatic. No biological data is given:

MECHANISM OF ACTION - **Tyrosine kinase** modulator;
Gene therapy.

USE - The human kinase polypeptide and nucleic acids are useful in developing human therapeutic and diagnostic compositions. These are also useful for screening for, diagnosing, preventing or treating hematopoietic disorders and other disorders associated with defective cell signal transduction, e.g. cancer. The agents that bind to the peptide are useful for treating a disease or condition mediated by a human kinase protein. (All claimed). (78 pages)

L22 ANSWER 2 OF 9 BIOTECHDS COPYRIGHT 2005 THE THOMSON CORP. on STN
ACCESSION NUMBER: 2002-15979 BIOTECHDS

TITLE: Nucleic acids encoding human phospholipase-D (PLD) proteins, useful for preventing, diagnosing and treating PLD-mediated disorders;
recombinant enzyme protein and sense and antisense gene use in disease therapy and gene therapy

AUTHOR: BEASLEY E M; YAN C; DI FRANCESCO V
PATENT ASSIGNEE: PE CORP NY
PATENT INFO: US 6368842 9 Apr 2002
APPLICATION INFO: US 2000-801052 15 Dec 2000
PRIORITY INFO: US 2001-801052 8 Mar 2001
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2002-370698 [40]

AB DERWENT ABSTRACT:

NOVELTY - Nucleic acids (I) encoding human phospholipase-D (PLD) proteins, are new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following: (1) an isolated nucleic acid molecule (I) encoding a phospholipase D protein, comprising: (a) a nucleotide sequence that encodes a protein comprising a defined 465 amino acid sequence (A1) given in the specification; (b) a nucleic acid molecule comprising the defined 1872 nucleotide sequence (N1) given in the specification; and (c) a nucleic acid molecule comprising the defined 16063 nucleotide sequence (N2) given in the specification; (2) a nucleic acid vector (II) comprising (I); (3) a host cell comprising (II); (4) a process for producing a polypeptide, comprising culturing (III) under conditions for the production of the polypeptide, and recovering the peptide from the host cell culture; and (5) an isolated nucleic acid molecule (I') consisting of a nucleotide sequence that is completely complementary to (I). Preparation: The nucleic acids and encoded polypeptides may be produced via standard recombinant or synthetic methodologies.

BIOTECHNOLOGY - Preferred Nucleic Acids: (I) Comprises N1 or N3 per se. Preferred Vector: The vector is a plasmid, a virus and/or a bacteriophage. (I) Is inserted into the vector in proper orientation and correct reading frame so that the protein A1 may be expressed by a cell transformed with the vector. (I) Is operatively linked to a promoter sequence.

ACTIVITY - None given.

MECHANISM OF ACTION - Gene therapy; Protein Therapy; Vaccine; Enzymatic (Phospholipase-D). Enzymes in the Phospholipase D (PLD) family catalyze the hydrolysis of phosphatidylcholine (PC) and other phospholipids to produce phosphatidic acid. A range of agonists acting through G protein-coupled receptors and receptor **tyrosine kinases** stimulate this hydrolysis. Phosphatidic acid appears to be important as a second messenger capable of activating a diverse range of signaling pathways. PC-specific PLD activity has been implicated in numerous cellular pathways, including signal transduction, membrane trafficking, the regulation of mitosis, regulated secretion, cytoskeletal reorganization, transcriptional regulation and cell-cycle control. Many proteins are attached to the plasma membrane via a glycosylphosphatidylinositol (GPI) anchor. Phosphatidylinositol-glycan (PIG)-specific PLDs selectively hydrolyze the inositol phosphate linkage, allowing release of the protein. The protein encoded by (I) is a novel human phospholipase splice form that is related to the phospholipase D (PLD) family. In particular, the novel phospholipase splice form provided by the present invention lacks exon 2 found in a prior art phospholipase protein. PLD proteins are known to exist as alternative splice forms (Steed et al., FASEB J. 1998 October; 12(13):1309-17). The phospholipase D family is characterized by a conserved HXKXXXXD motif and this characteristic motif is essential for the catalytic function of PLD. A subclass of PLD exists that is characterized by a second HXKXXXXD motif with a conserved Asp to Glu substitution. PLD enzymes play important roles in signal transduction and membrane vesicular trafficking in mammalian cells (Pedersen et al., J Biol Chem Nov. 20, 1998; 273(47):31494-504). In particular, PLD cleaves phosphatidylcholine in response to cell stimuli, therefore releasing phosphatidic acid, which is involved in numerous cellular responses that may play a role in, for example, regulation of secretion, mitogenesis, or cytoskeletal changes

(Steed et al., FASEB J. 1998 October; 12(13):1309-17). The activity and regulation of recombinant human PLD2 are identical to that of recombinant mouse PLD2. Analysis of the amino acid sequences of the human PLD1 and PLD2 isoforms revealed Pleckstrin homology domains. (Steed et al., FASEB J. 1998 October; 12(13):1309-17). Orthologs of PLD may exist in vaccinia virus (Pedersen et al., J Biol Chem Nov. 20, 1998; 273(47):31494-504). No biological data given.

USE - (I) And the protein it encodes may be used in the prevention, diagnosis and treatment of diseases associated with inappropriate PLD expression. For example, (I) (or (II)) and PLD may be used to treat disorders associated with decreased expression by rectifying mutations or deletions in a patient's genome that affect the activity of PLD by expressing inactive proteins or to supplement the patients own production of PLD. (I) May be used to produce PLD, by inserting the nucleic acids into a host cell (III) and culturing (IV) the cell to express the PLD protein (claimed). (I) And its complement (I') may also be used as DNA probes in diagnostic assays to detect and quantitate the presence of similar nucleic acids in samples, and therefore which patients may be in need of restorative therapy. The PLD polypeptide may also be used as antigens in the production of antibodies against PLD and in assays to identify modulators of PLD expression and activity. The anti-PLD antibodies and antagonists may also be used to down regulate expression and activity. The anti-PLD antibodies may also be used as diagnostic agents for detecting the presence of PLD in samples (e.g. by enzyme linked immunosorbant assay (ELISA)). No examples of disease that may be treated are given.

ADMINISTRATION - Standard routes.

ADVANTAGE - Phospholipase proteins, particularly members of the phospholipase D subfamily, are a major target for drug action and development. It is valuable to the field of pharmaceutical development to identify and characterize previously unknown members of this subfamily of phospholipase proteins. The nucleic acids advance the state of the art by providing previously unidentified human phospholipase proteins that have homology to members of the phospholipase D subfamily.

EXAMPLE - No examples given. (30 pages)

L22 ANSWER 3 OF 9 BIOTECHDS COPYRIGHT 2005 THE THOMSON CORP. on STN

ACCESSION NUMBER: 2002-07016 BIOTECHDS

TITLE: Nucleic acids encoding a proto-oncogene **tyrosine kinase**, useful for the prevention, diagnosis and treatment of e.g. leukemia and lung tumors;

tyrosine-kinase gene transfer by

vector expression in host cell for cancer gene therapy

AUTHOR: **GAN W; YE J; DI FRANCESCO V; BEASLEY E M**

PATENT ASSIGNEE: PE CORP NY

PATENT INFO: US 6340584 22 Jan 2002

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NOVELTY - Isolated nucleic acid sequences (I) encoding a proto-oncogene **tyrosine kinase** (poTK), is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following: (1) an isolated nucleic acid molecule (I) comprising a nucleotide sequence selected from: (a) a nucleotide sequence that encodes a defined 752 amino acid sequence (A1) given in the specification; (b) a nucleic acid molecule comprising a defined 2674 nucleotide sequence (N1) given in the specification; (c) a nucleic acid molecule consisting of a defined 15297 nucleotide sequence (N2) given in the specification; and (d) a nucleotide sequence that is completely complementary to a

nucleotide sequence of (a)-(c); (2) a nucleic acid vector (II) comprising (I); (3) a host cell (IV) containing (III); and (4) a process (V) for producing a polypeptide comprising culturing the host cell (IV) under conditions sufficient for the production of the polypeptide, and recovering the peptide from the host cell culture.

BIOTECHNOLOGY - Preferred Nucleic Acid Molecules: (I) Comprises (N1) or (N2). Preferred Vectors: (II) Is a plasmid, virus or bacteriophage. The isolated nucleic acid molecule is inserted into the vector in proper orientation and correct reading frame so that the protein of (A1) may be expressed by a cell transformed with the vector. The isolated nucleic acid molecule is operatively linked to a promoter sequence. Preparation: (I) Has been isolated from human placenta, lung tumors, kidney tumors, pregnant uterus, leukemia, stomach adenocarcinoma, and hippocampus, via standard methodologies. The poTK it encodes may be produced by culturing (IV).

ACTIVITY - Cytostatic; Anti-leukemic. No biological data given.

MECHANISM OF ACTION - Gene therapy; Protein therapy; Vaccine; Enzymatic-inhibition; Anti-kinase.

USE - (I) and the poTK may be used in the prevention, diagnosis and treatment of diseases associated with inappropriate poTK expression, such as lung and kidney tumors, leukemia and stomach adenocarcinoma. For example, (I) (or (II)) and poTK may be used to treat disorders associated with decreased expression by rectifying mutations or deletions in a patient's genome that affect the activity of poTK by expressing inactive proteins or to supplement the patients own production of poTK. Additionally, (I) and (II) may be used to produce the poTK, by inserting the nucleic acid into a host cell (III) and culturing the cell to express the protein (V). (I) and its complementary sequences may also be used as DNA probes in diagnostic assays to detect and quantitate the presence of similar nucleic acids in samples, and therefore which patients may be in need of restorative therapy. The encoded poTK may be used as an antigen in the production of antibodies against poTK and in assays to identify modulators of poTK expression and activity. The anti-poTK antibodies and antagonists may be used to down regulate expression and activity and as diagnostic agents for detecting the presence of poTK in samples.

ADMINISTRATION - No details given. (49 pages).

L22 ANSWER 4 OF 9 BIOTECHDS COPYRIGHT 2005 THE THOMSON CORP. on STN

ACCESSION NUMBER: 2002-08356 BIOTECHDS

TITLE: New isolated human kinase proteins useful for the prevention, diagnosis and treatment of kinase-related disorders; vector-mediated gene transfer and expression in host cell for recombinant protein production and gene therapy

AUTHOR: YE J; KETCHUM K A; DI FRANCESCO V; BEASLEY E
M

PATENT ASSIGNEE: PE CORP NY

PATENT INFO: US 6323016 27 Nov 2001

APPLICATION INFO: US 2000-799345 9 Jun 2000

PRIORITY INFO: US 2001-799345 6 Mar 2001

DOCUMENT TYPE: Patent

LANGUAGE: English

OTHER SOURCE: WPI: 2002-096591 [13]

AB DERWENT ABSTRACT:

NOVELTY - Isolated human kinase proteins, (I,) and encoding nucleic acid molecules (II), are new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following: (1) an isolated nucleic acid molecule (I) encoding a **tyrosine kinase** comprising a nucleotide sequence selected from: (a) a nucleotide sequence that encodes a polypeptide comprising a defined 295 amino acid sequence (A1) given in the specification; (b) a nucleic acid molecule comprising a defined 2532 nucleotide nucleic acid sequence (N1) given in the specification; and (c) a nucleic acid molecule comprising a defined 8758 nucleotide nucleic acid

sequence (N2) given in the specification; (2) a nucleic acid vector (II) comprising (I); (3) a host cell (III) containing the vector (II); (4) a method (IV) for detecting the presence of (I) in a sample, said method comprising contacting the sample with an oligonucleotide comprising at least 20 contiguous nucleotides that hybridizes to the nucleic acid molecule under stringent conditions (hybridization in 6 x sodium chloride/sodium citrate (SSC) at 45 degreesC, followed by one or more washes in 0.2 x SCC, 0.1% SDS at 50-65 degreesC), and determining whether the oligonucleotide binds to the nucleic acid molecule in the sample; (5) a process (V) for producing a polypeptide comprising culturing the host cell (III) conditions sufficient for the production of the polypeptide, and recovering the peptide from the host cell culture; and (6) an isolated nucleic acid molecule (VI) comprising a nucleotide sequence that is completely complementary to (I).

WIDER DISCLOSURE - Antibodies against the kinases are also disclosed.

BIOTECHNOLOGY - Preparation: (I) is produced via (V). Preferred Nucleic Acids: (I) Comprises (N1) or (N2). Preferred Vector: The vector (II) is a plasmid, virus or bacteriophage. The isolated nucleic acid molecule is inserted into the vector in proper orientation and correct reading frame so that the protein of (A1) may be expressed by a cell transformed with the vector. The isolated nucleic acid molecule is operatively linked to a promoter sequence.

ACTIVITY - No details given.

MECHANISM OF ACTION - Gene therapy; kinase modulation. No biological data given.

USE - (I) and (II) may be used in the prevention, diagnosis and treatment of diseases associated with inappropriate kinase expression. For example, (II) (or (III)) and (I) may be used to treat disorders associated with decreased expression by rectifying mutations or deletions in a patient's genome that affect the activity of kinase by expressing inactive proteins or to supplement the patients own production of kinases. Additionally, (II) may be used to produce the kinase polypeptide, by inserting the nucleic acids into a host cell (III) and culturing the cell to express the protein (V). (II) and its complement (VII) may also be used as DNA probes in diagnostic assays to detect and quantitate the presence of similar nucleic acids in samples, and therefore which patients may be in need of restorative therapy. The polypeptides may also be used as antigens in the production of antibodies against (I) and in assays to identify modulators of kinase expression and activity. The anti-(I) antibodies and antagonists may also be used to down regulate expression and activity. The anti-(I) antibodies may also be used as diagnostic agents for detecting the presence of (I) in samples (e.g. by enzyme linked immunosorbant assay (ELISA)).

ADMINISTRATION - Administration is by standard methodology. No dosage details given. (38 pages)

L22 ANSWER 5 OF 9 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED.
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ACCESSION NUMBER: 2003456872 EMBASE

TITLE: Erratum: Reassembly of the tight junction after oxidative stress depends on **tyrosine kinase** activity (Journal of Biological Chemistry (2001) 276 (22048-22055)).

AUTHOR: Meyer T.N.; Schwesinger C.; **Ye J.**; Denker B.M.; Nigam S.K.

SOURCE: Journal of Biological Chemistry, (23 Nov 2001) Vol. 276, No. 47, pp. 44354-44355.
ISSN: 0021-9258 CODEN: JBCHA3

COUNTRY: United States

DOCUMENT TYPE: Journal; Errata

FILE SEGMENT: 029 Clinical Biochemistry

LANGUAGE: English

ENTRY DATE: Entered STN: 20031211
Last Updated on STN: 20031211

L22 ANSWER 6 OF 9 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2001363955 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11294856
TITLE: Reassembly of the tight junction after oxidative stress depends on **tyrosine kinase** activity.
AUTHOR: Meyer T N; Schwesinger C; **Ye J**; Denker B M; Nigam S K
CORPORATE SOURCE: Renal Division, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts 02115, USA.
CONTRACT NUMBER: DK53507 (NIDDK)
GM55223 (NIGMS)
SOURCE: Journal of biological chemistry, (2001 Jun 22) 276 (25) 22048-55. Electronic Publication: 2001-04-09.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200107
ENTRY DATE: Entered STN: 20010723
Last Updated on STN: 20030105
Entered Medline: 20010719

AB Oxidative stress compromises the tight junction, but the mechanisms underlying its recovery remain unclear. We developed a model in which oxidative stress reversibly disrupts the tight junction. Exposure of Madin-Darby canine kidney cells to hydrogen peroxide markedly reduced transepithelial resistance and disrupted the staining patterns of the tight junction proteins ZO-1 and occludin. These changes were reversed by catalase. The short-term reassembly of tight junctions was not dependent on new protein synthesis, suggesting that recovery occurs through re-utilization of existing proteins. Although ATP levels were reduced, the reduction was insufficient to explain the observed changes, since a comparable reduction of ATP levels (with 2-deoxy-D-glucose) did not induce these changes. The intracellular hydrogen peroxide scavenger pyruvate protected Madin-Darby canine kidney cells from loss of transepithelial resistance as did the heavy metal scavenger N,N,N',N'-tetrakis(2-pyridylmethyl)ethylenediamine. Of a wide variety of agents examined, only **tyrosine kinase** inhibitors and protein kinase C inhibitors markedly inhibited tight junction reassembly. During reassembly, tyrosine phosphorylation in or near the lateral membrane, was detected by immunofluorescence. The **tyrosine kinase** inhibitors genistein and PP-2 inhibited the recovery of transepithelial resistance and perturbed the relocalization of ZO-1 and occludin to the tight junction, indicating that **tyrosine kinases**, possibly members of the Src family, are critical for reassembly after oxidative stress.

L22 ANSWER 7 OF 9 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2001571345 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11678602
TITLE: Cr (VI) increases tyrosine phosphorylation through reactive oxygen species-mediated reactions.
AUTHOR: Qian Y; Jiang B H; Flynn D C; Leonard S S; Wang S; Zhang Z; **Ye J**; Chen F; Wang L; Shi X
CORPORATE SOURCE: Cancer Center and Department of Microbiology and Immunology, School of Medicine, West Virginia University, Morgantown 26506, USA.
SOURCE: Molecular and cellular biochemistry, (2001 Jun) 222 (1-2) 199-204.

Journal code: 0364456. ISSN: 0300-8177.

PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200202
ENTRY DATE: Entered STN: 20011029
Last Updated on STN: 20020228
Entered Medline: 20020227

AB While Cr (VI)-containing compounds are well established carcinogens, the mechanisms of their action remain to be investigated. In this study we show that Cr (VI) causes increased tyrosine phosphorylation in human lung epithelial A549 cells in a time-dependent manner. N-acetyl-cysteine (NAC), a general antioxidant, inhibited Cr (VI)-induced tyrosine phosphorylation. Catalase, a scavenger of H₂O₂, sodium formate and aspirin, scavengers of hydroxyl radical (*OH), also inhibited the increased tyrosine phosphorylation induced by Cr (VI). SOD, an inhibitor of superoxide radical (O₂*-), caused less inhibition. ESR study shows that incubation of Cr (VI) with the A549 cells generates *OH radical. The generation of radical was decreased by addition of catalase and sodium formate, while SOD did not have any inhibitory effect. Oxygen consumption measurements show that addition of Cr (VI) to A549 cells resulted in enhanced molecular oxygen consumption. These results indicate that Cr (VI) can induce an increase in tyrosine phosphorylation. H₂O₂ and *OH radicals generated during the process are responsible for the increased tyrosine phosphorylation induced by Cr (VI).

L22 ANSWER 8 OF 9 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 95370702 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7643015
TITLE: Cellular and molecular mechanisms of IFN-gamma production induced by IL-2 and IL-12 in a human NK cell line.
AUTHOR: Ye J; Ortaldo J R; Conlon K; Winkler-Pickett R; Young H A
CORPORATE SOURCE: Laboratory of Experimental Immunology, NCI-FCRDC, Frederick, Maryland 21702-1201, USA.
SOURCE: Journal of leukocyte biology, (1995 Aug) 58 (2) 225-33.
Journal code: 8405628. ISSN: 0741-5400.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199509
ENTRY DATE: Entered STN: 19950930
Last Updated on STN: 19950930
Entered Medline: 19950918

AB Interferon-gamma (IFN-gamma) is an important immunoregulatory protein produced predominantly by T cells and large granular lymphocytes (LGL) in response to different extracellular signals. In particular, two interleukins (ILs), IL-2 and IL-12, have been shown to be potent inducers of IFN-gamma gene expression in both T cells and LGL. Although it has been reported that there are some T cell lines that produce IFN-gamma in response to IL-2 and IL-12 stimulation, there has as yet been no report of a natural killer (NK) cell line that responds in a similar manner. In this report we present evidence that the cell line NK3.3 derived from human NK cells, responds to both IL-2 and IL-12, as measured by increases in IFN-gamma and granulocyte-macrophage colony-stimulating factor (GM-CSF) cytoplasmic mRNA and protein expression. In addition, when used together IL-2 and IL-12 synergized in the induction of IFN-gamma and GM-CSF and this synergy was attributed to an increased accumulation and stability of the IFN-gamma and GM-CSF mRNAs. To investigate the signaling pathways involved in the gene induction, five inhibitors, cyclosporin A (CsA), transforming growth factor-beta, cycloheximide, genistein, and

staurosporine A, were used in analyzing the effects of IL-2 and IL-12 on NK3.3 cells. The results suggest that activation of protein kinase C, but not new protein synthesis, is required for IL-2 induction of IFN-gamma and GM-CSF cytoplasmic mRNA. In contrast, IL-12 induction of IFN-gamma cytoplasmic mRNA appears to only partially depend on activation of protein kinase C. Furthermore, both transforming growth factor-beta and genistein, a **tyrosine kinase** inhibitor, could suppress IL-2 and IL-12 signaling but CsA was generally inactive. It also was observed that suppression of cytokine gene expression by these agents was independent of the inhibition of proliferation. In addition, IL-2 but not IL-12 induced nuclear factors NF-kappa B and AP1, and regulation of the nuclear levels of these two DNA binding protein complexes is correlated with IFN-gamma and GM-CSF gene expression. These data indicate that IL-2 and IL-12 may have distinct signaling pathways leading to the induction of IFN-gamma and GM-CSF gene expression, and that the NK3.3 cell line may serve as a novel model for dissecting the biochemical and molecular events involved in these pathways.

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ACCESSION NUMBER: 95033501 EMBASE
DOCUMENT NUMBER: 1995033501
TITLE: Identification of a DNA binding site for the nuclear factor YY1 in the human GM-CSF core promoter.
AUTHOR: Ye J.; Young H.A.; Ortaldo J.R.; Ghosh P.
CORPORATE SOURCE: Laboratory Experimental Immunology, Biological Response Modifier Program, DCT, NCI-FCRDC, Frederick, MD 21702-1201, United States
SOURCE: Nucleic Acids Research, (1994) Vol. 22, No. 25, pp. 5672-5678.
ISSN: 0305-1048 CODEN: NARHAD
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 022 Human Genetics
025 Hematology
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 950215
Last Updated on STN: 950215

AB It has been well documented that the repeated CATT(A/T) sequence, localized between -64 and -35 in the human GM-CSF promoter, is required for the promoter activity, and this region likely serves as a core recognition sequence for a cellular transcription factor. However, the transcription factor that interacts with this site was not identified. Here, we report that this element contains a binding site for the nuclear factor YY1, which has not been reported to play a role in the regulation of cytokine gene transcription. Results from transient transfection assays of the Jurkat T cell line revealed that this repeated CATT(A/T) element exhibited enhancer activity when linked to both the human IFN-gamma promoter and the TK promoter. Mutation of the YY1 binding site eliminated about 60% of the enhancer activity of the element. We have found that the YY1 binding site could form two specific DNA-protein complexes, A and B, with Jurkat nuclear proteins in the electrophoretic mobility shift assay and that the binding of these complexes correlates with the enhancer activity. UV cross-linking analysis revealed that the A complex is a multi-protein complex and in addition to YY1, other proteins are required for formation of the protein complex. Cotransfection assays with a YY1 expression vector revealed that overexpression of YY1 resulted in an inhibitory effect on the repeated CATT(A/T) element, indicating that in addition to YY1, cofactors also are required for the activator function of the A complex.

=> d his

(FILE 'HOME' ENTERED AT 12:43:08 ON 02 AUG 2005)

FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS, LIFESCI' ENTERED AT 12:43:44 ON 02 AUG 2005

L1	219065	S	TYROSINE (A) KINASE?
L2	117272	S	PROTO(W) ONCOGENE
L3	19359	S	L1 AND L2
L4	11988	S	HUMAN AND L3
L5	7194083	S	CLON? OR EXPRESS? OR RECOMBINANT
L6	8010	S	L4 AND L5
L7	1361302	S	UTERUS OR LEUKEMIA OR ADENOCARCINOMA
L8	1451	S	L6 AND L7
L9	5	S	L8 AND HIPPOCAMPUS
L10	67	S	L2(W) L1
L11	33	DUP REM	L10 (34 DUPLICATES REMOVED) E GAN W/AU
L12	98	S	E3 E DIFRANCESCO V/AU
L13	97	S	E3-E4 E BEASLEY E M/AU
L14	330	S	E3 E YE J/AU
L15	1947	S	E3
L16	2366	S	L12 OR L13 OR L14 OR L15
L17	1	S	L4 AND L16
L18	19359	S	L1 AND L3
L19	1	S	L16 AND L18
L20	1	S	L16 AND L3
L21	12	S	L1 AND L16
L22	9	DUP REM	L21 (3 DUPLICATES REMOVED)

	L #	Hits	Search Text
1	L1	16005	tyrosine adj kinase\$2
2	L2	4449	proto adj oncogene
3	L3	801	l1 same l2
4	L4	75511 2	clon\$3 or express\$3 or recombinant
5	L5	331	l3 same l4
6	L6	49782 7	human
7	L7	163	l5 same l6
8	L8	56976	uterus or leukemia or adenocarcinoma
9	L9	55	l7 same l8
10	L10	23308	BEASLEY YE GAN DIFRANCESCO
11	L11	18	l3 and l10

	Issue Date	Pages	Document ID	Title
1	20050602	66	US 20050119536 A1	Diagnostics and therapeutics for arterial wall disruptive disorders
2	20050414	40	US 20050079547 A1	Protein fragment complementation assays in whole animals applications to drug efficacy, ADME, cancer biology, immunology, infectious disease and gene therapy
3	20050414	18	US 20050079508 A1	Constraints-based analysis of gene expression data
4	20050317	55	US 20050059153 A1	Electromagnetic activation of gene expression and cell growth
5	20050217	95	US 20050037430 A1	Methods and uses for protein breakdown products
6	20050120	26	US 20050015206 A1	Nucleic acid detection assay control genes
7	20041125	19	US 20040234527 A1	Peptides for use as translocation factors
8	20041111	25	US 20040224967 A1	Phenylaminopyrimidine derivatives and methods of use
9	20040923	135	US 20040185485 A1	Gene markers useful for detecting skin damage in response to ultraviolet radiation
10	20040408	25	US 20040067951 A1	6-aryl-imidazo[1,2-a]pyrazin-8-ylamines, method of making, and method of use thereof
11	20040401	53	US 20040063130 A1	Isolated human kinase proteins, nucleic acid molecules encoding human kinase proteins, and uses thereof
12	20040226	266	US 20040038917 A1	Gene expression in biological conditions

	Issue Date	Pages	Document ID	Title
13	20040226	35	US 20040038298 A1	Protein fragment complementation assays for the detection of biological or drug interactions
14	20040226	259	US 20040038207 A1	Gene expression in bladder tumors
15	20040219	88	US 20040033502 A1	Gene expression profiles in esophageal tissue
16	20040219	324	US 20040033495 A1	Methods of diagnosis of angiogenesis, compositions and methods of screening for angiogenesis modulators
17	20040205	71	US 20040023231 A1	System for identifying and analyzing expression of are-containing genes
18	20040129	111	US 20040018513 A1	Classification and prognosis prediction of acute lymphoblastic leukemia by gene expression profiling
19	20040108	52	US 20040005612 A1	Endometrial genes in endometrial disorders
20	20031016	37	US 20030194721 A1	Genes expressed in treated foam cells
21	20031002	40	US 20030187225 A1	Antibody fusion proteins: effective adjuvants of protein vaccination
22	20030918	259	US 20030175771 A1	Human Transcriptomes
23	20030807	64	US 20030149997 A1	Diagnostics and therapeutics for arterial wall disruptive disorders
24	20030612	83	US 20030110525 A1	Neurturin receptor

	Issue Date	Pages	Document ID	Title
25	20030508	155	US 20030087816 A1	Novel proteins and nucleic acids encoding same
26	20030417	179	US 20030073888 A1	Screening methods used to identify compounds that modulate a response of a cell to ultraviolet radiation exposure
27	20030320	22	US 20030054387 A1	Metastasis-associated genes
28	20030313	35	US 20030049688 A1	Protein fragment complementation assays for the detection of biological or drug interactions
29	20030130	65	US 20030022284 A1	Uses of GDNF and GDNF receptor
30	20021114	53	US 20020168741 A1	Isolated human kinase proteins, nucleic acid molecules encoding human kinase proteins, and uses thereof
31	20021024	41	US 20020155527 A1	C-erbB-2 external domain: gp75
32	20021024	166	US 20020155115 A1	Novel proteins and nucleic acids encoding same
33	20020711	128	US 20020090624 A1	Gene markers useful for detecting skin damage in response to ultraviolet radiation
34	20020502	72	US 20020051972 A1	NEURTURIN RECEPTOR
35	20040921	110	US 6794137 B2	Gene markers useful for detecting skin damage in response to ultraviolet radiation
36	20040817	80	US 6777196 B2	Neurturin receptor

	Issue Date	Pages	Document ID	Title
37	20040203	50	US 6686187 B2	Isolated human kinase proteins, nucleic acid molecules encoding human kinase proteins, and uses thereof
38	20040106	89	US 6673902 B2	Cyclin D binding factor, and uses thereof
39	20030819	50	US 6607879 B1	Compositions for the detection of blood cell and immunological response gene expression
40	20030610	24	US 6576812 B1	Compound screening assays using a transgenic mouse model of human skin diseases
41	20030225	10	US 6524787 B1	Diagnostics and therapy based on vascular mimicry
42	20030107	62	US 6504007 B1	GDNF receptor
43	20020806	31	US 6428951 B1	Protein fragment complementation assays for the detection of biological or drug interactions
44	20020416	79	US 6372453 B1	Neurturin receptor
45	20020326	130	US 6361976 B1	Co-administration of interleukin-3 mutant polypeptides with CSF'S for multi-lineage hematopoietic cell production
46	20020129	79	US 6342348 B1	Neurturin receptor
47	20020122	50	US 6340584 B1	Isolated human kinase proteins, nucleic acid molecules encoding human kinase proteins, and uses thereof
48	20020101	227	US 6335170 B1	Gene expression in bladder tumors

	Issue Date	Pages	Document ID	Title
49	20010925	41	US 6294330 B1	Protein fragment complementation assays for the detection of biological or drug interactions
50	20010807	31	US 6270964 B1	Protein fragment complementation assays for the detection of biological or drug interactions
51	20000215	78	US 6025157 A	Neurturin receptor
52	19990112	108	US 5858347 A	Therapeutic methods using fusion proteins between interleukin-3 (IL-3) variants and other hematopoietic factors
53	19970805	27	US 5654406 A	Antibody to ERBB2 promoter binding factor
54	19960521	27	US 5518885 A	ERBB2 promoter binding protein in neoplastic disease
55	19940920	29	US 5348856 A	DNA encoding TRKC protein

	Issue Date	Pages	Document ID	Title
1	20050721	148	US 20050158737 A1	Tumour associated antigens
2	20040603	53	US 20040107453 A1	Multipotent adult stem cells, sources thereof, methods of obtaining same, methods of differentiation thereof, methods of use thereof and cells derived thereof
3	20040506	56	US 20040086485 A1	Chemeric viral vectors for gene therapy
4	20040408	248	US 20040068095 A1	Novel human proteins, polynucleotides encoding them and methods of using the same
5	20040401	53	US 20040063130 A1	Isolated human kinase proteins, nucleic acid molecules encoding human kinase proteins, and uses thereof
6	20040108	345	US 20040005563 A1	Methods of diagnosis of ovarian cancer, compositions and methods of screening for modulators of ovarian cancer
7	20030605	99	US 20030105000 A1	Methods and compositions for inhibiting GRB7
8	20030306	36	US 20030045499 A1	Dendritic cells transduced with a wild-type self gene elicit potent antitumor immune responses
9	20030227	25	US 20030039656 A1	Modified reoviral therapy
10	20021205	69	US 20020183271 A1	Methods of treatment involving human MDA-7

	Issue Date	Pages	Document ID	Title
11	20021114	53	US 20020168741 A1	Isolated human kinase proteins, nucleic acid molecules encoding human kinase proteins, and uses thereof
12	20050308	37	US 6864286 B2	Inhibitors of the EGF-receptor tyrosine kinase and methods for their use
13	20040224	18	US 6696241 B2	Measuring esterase activity using fluorescent substrates as a way of evaluating cervical cancer
14	20040203	50	US 6686187 B2	Isolated human kinase proteins, nucleic acid molecules encoding human kinase proteins, and uses thereof
15	20020122	50	US 6340584 B1	Isolated human kinase proteins, nucleic acid molecules encoding human kinase proteins, and uses thereof
16	20000307	75	US 6034212 A	SH3 kinase domain associated protein, a signalling domain therein, nucleic acids encoding the protein and the domain, and diagnostic and therapeutic uses thereof
17	20000208	59	US 6022740 A	SH3 kinase domain associated protein, a signalling domain therein, nucleic acids encoding the protein and the domain, and diagnostic and therapeutic uses thereof
18	19990302	54	US 5877309 A	Antisense oligonucleotides against JNK